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(54) **Useful Combinations of Monobactam Antibiotics with beta-Lac-tamase Inhibitors**

Nützliche Kombinationen aus Monobactam-Antibiotika mit beta-Lactamase-Hemmern

Combinaisons utiles d'antibiotiques au monobactam avec des initiateurs de la bêta-lac-tamase

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EP 2 484 680 B1

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Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

Description

Field of the invention

[0001] The present invention is concerned with pharmaceutical compositions and methods for treating infections caused by pathogenic Gram-negative bacteria.

Background of the invention

[0002] β-Lactam antibiotics have been widely used for the treatment of bacterial infections both in hospitals and in the general public. There are several classes of β-lactam antibiotics that have found clinical application, these include the penicillins, cephalosporins, cephamycins, carbacephems, oxacephems, carbapenems and monobactams.

[0003] The efficiency of all of these classes to cure bacterial infections has been impaired by the appearance of bacteria that are resistant towards the antibiotics. The prevalent cause of this resistance in Gram-negative bacteria is the expression by the bacteria of enzymes known as β-lactamase that are able to hydrolyse the β-lactam antibiotics rendering them inactive. Bacteria are able to produce a variety of β-lactamases, including penicillinases, cephalosporinases, cephamycinases, carbapenemases, monobactamases, broad-spectrum β-lactamases and extended-spectrum β-lactamases.

[0004] The possibility of rescuing individual β-lactam antibiotics by combination with a β-lactamase inhibitor that inactivates the β-lactamase before it can hydrolyse the β-lactam antibiotic has been demonstrated with clinically useful combinations between penicillins such as amoxicillin, ampicillin and ticarcillin and β-lactamase inhibitors such as clavulanic acid, sulbactam and tazobactam. Further, potential combinations have been described involving cephalosporins and newly developed β-lactamase inhibitors including bridged monobactams, penam sulfones, phosphonate esters, exomethylene penams and diazabicyclooctane derivatives.

[0005] Monobactams have been regarded as stable towards many β-lactamases. However, there are now many strains of Gram-negative bacteria that exhibit β-lactamase-mediated resistance towards the monobactam antibiotics (aztreonam, carumonam and tigemonam).

[0006] WO 02/22613 discloses in example 1 the monobactam antibiotic (3*S*,4*S*)-3-{(2*Z*)-2-(2-amino(1,3-thiazol-4-yl))-3- [(1,5-dihydroxy-4-oxo(2-hydropyridyl))methoxy]-3-azaprop-2-enoylamino}-4-methyl-2-oxoazetidinesulfonic acid, designated in the instant application as "compound 1" or "antibiotic 1".

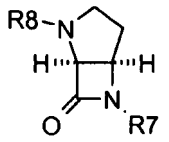
[0007] The present invention aims to provide improved medicaments with novel monobactam antibiotics and combinations of monobactam antibiotics with β-lactamase inhibitors that are active against aerobic Gram-negative bacteria that are resistant against treatments with monobactam antibiotics.

Summary of the invention

[0008] The objective set is solved by the monobactams of claims 1-3.

[0009] β-lactamase inhibitors are according to the following groups b1) to b11):

b1) a bridged monobactam derivative of the following formula II:



II

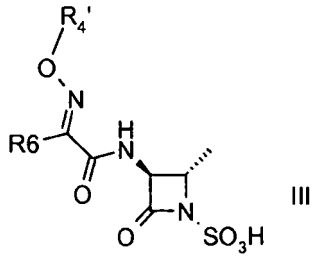
in which:

R7 signifies SO_3H, OSO_3H or OCRjRj'COOH,
wherein Rj and Rj' are independently selected from hydrogen; alkyl; phenyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkoxy, amino, alkylamino, dialkylamino and halogen; benzyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkoxy, amino, alkylamino, dialkylamino and halogen; alkylamino and alkoxyalkyl;
R8 is alkoxycarbonylamino, the acyl residue of an α or β-amino acid, or a residue of the formula Q-$(X)_r$-Y-,
wherein Q is a 3-6 membered ring which optionally contains nitrogen, sulphur and/or oxygen and which is optionally fused to a phenyl ring or to a 5-6 membered heterocyclic ring and which is optionally substituted with 1 to 4 substituents selected from alkyl, allyl, hydroxyl, alkoxy, amino, alkylamino, dialkylamino, carboxamide

which may be substituted, carboxylic acid, carbonylalkoxy, aminocarbonyl, alkylaminocarbonyl, halogen, halogenomethyl, dihalogenomethyl, trihalogenomethyl, sulfamide, substituted sulfamide with substituents selected from alkyl, allyl, phenyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkoxy, amino, alkylamino and halogen and benzyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkoxy, amino, alkylamino, halogen and benzyl, urea which may be substituted with alkyl, aminoalkyl or alkoxy and carbamate which may be substituted with alkyl, aminoalkyl or alkoxy, X signifies a linear spacer of from 1 to 6 atoms length and containing carbon, nitrogen, oxygen and/or sulphur atoms, of which up to 2 atoms can be nitrogen atoms and 1 atom can be oxygen or sulphur,
r is an integer of from 0 to 1; and
Y is selected from -CO-, -CS-, -NHCO-, -NHCONH- and -SO_2-; or a pharmaceutically acceptable salt thereof,

or

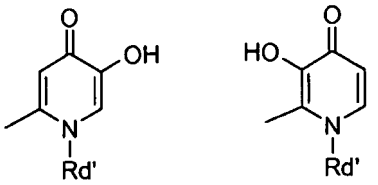
b2) a monobactam derivative of the general formula III:



III

in which

R4' signifies hydrogen, alkyl or CH(Rx')Z', wherein
Rx' is selected from hydrogen; (C_1-C_6)alkyl; allyl; phenyl and (C_3-C_6)cycloalkyl; and Z' signifies COOH or a group of one of the following two formulae:



in which Rd' is hydrogen or hydroxy; and
R6 is as defined for formula I; or a pharmaceutically acceptable salt thereof,

or

b3) a penam sulfone derivative of the general formulae IV or V:



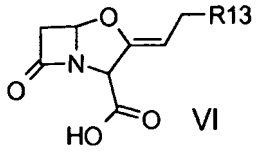
in which

R9 signifies COOH or a 5-6 membered monocyclic or polycyclic heteroaromatic group;
R10 signifies hydrogen or halogen;

R11 signifies CH_2R12; CH=CHR12 wherein R12 is hydrogen, halogen, cyano, carboxylic acid, acyl such as acetyl, carboxamide which may be substituted, alkoxycarbonyl or a 5-6 membered heteroaromatic ring which is optionally substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkoxy, amino, alkylamino, dialkylamino and halogen; or which is optionally fused with a 5-6 membered heteroaromatic ring; CH=NR12' wherein R12' is amino, alkylamino, dialkylamino, aminocarbonyl, acylamino such as acetylamino, hydroxy, alkoxy,

or a pharmaceutically acceptable salt thereof;
or

b4) an oxapenam derivative of the general formula VI:



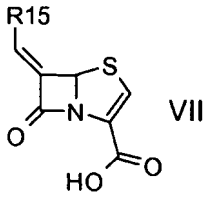
VI

in which

R13 signifies OR14; $S(O)_nR14$ or a 5-6 membered heteroaromatic ring which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkoxy, amino, alkylamino, dialkylamino and halogen; whereby n = 0, 1 or 2, and R14 is hydrogen, alkyl, (C_2-C_7) alkene, (C_2-C_7 alkyne or a 5-6 membered heteroaromatic ring which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkoxy, amino, alkylamino, dialkylamino and halogen,

or a pharmaceutically acceptable salt thereof;
or

b5) a penem derivative of the general formula VII:



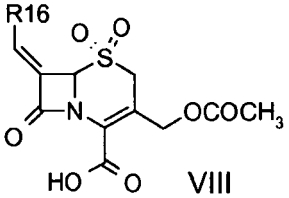
VII

in which

R15 signifies a 5-6 membered heteroaromatic ring which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkoxy, amino, alkylamino, dialkylamino and halogen; or which is optionally fused with a 5-6 membered heteroaromatic ring and/or which is optionally bound to the exo-methylene group over a -CH=CH- spacer being preferably in the (E)-configuration,

or a pharmaceutically acceptable salt thereof;
or

b6) a cephem sulfone derivative of the general formula VIII:



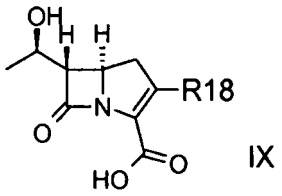
VIII

in which

R16 signifies COOR17, whereby R17 signifies hydrogen or alkyl; or a 5-6 membered heteroaromatic ring which is optionally fused with a 5-6 membered heteroaromatic ring being optionally substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkoxy, amino, alkylamino, dialkylamino, halogen; and/or being optionally bound to the exo-methylene group over a -CH=CH- spacer being preferably in the (E)-configuration,

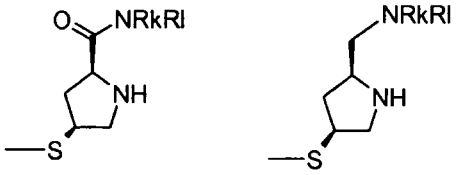
or a pharmaceutically acceptable salt thereof;
or

b7) meropenem, ertapenem, doripenem or a carbapenem derivative of the general formula IX:



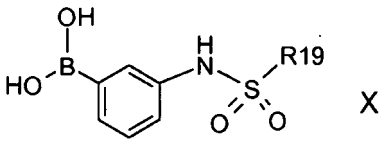
IX

in which R18 signifies -S-alkyl, -S-$(CH_2)_2$-NH-CH=NH or a group of the following two formulae



wherein Rk and R1 are individually selected from hydrogen, alkyl, 2-, 3-, 4-carboxyphenyl and sulfamoyl, or a pharmaceutically acceptable salt thereof;
or

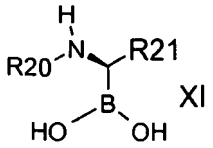
b8) a boronate derivative of the general formula X:



X

wherein R19 signifies a 5-6 membered heteroaromatic ring which may be substituted with amino, alkylamino, dialkylamino or alkylsulfoxide, or a pharmaceutically acceptable salt thereof;
or

b9) a boronate derivative of the general formula XI:



XI

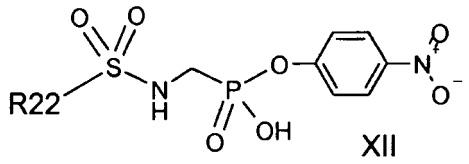
wherein

R20 and 21 are independently selected from a 5-6 membered heteroaromatic ring or phenyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkoxy, amino, alkylamino, dialkylamino and halogen and benzyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkoxy,

amino, alkylamino, dialkylamino and halogen,

or a pharmaceutically acceptable salt thereof;
or

b10) a phosphonate derivative of the general formula XII:



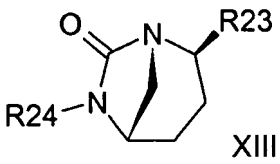
XII

wherein

R22 is selected from a 5-6 membered heteroaromatic ring which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkoxy, amino, alkylamino, dialkylamino and halogen and which is optionally fused with a 5-6 membered heteroaromatic ring; phenyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkoxy, amino, alkylamino, dialkylamino and halogen; and benzyl which may be substituted with 1 to 5 substituents selected from alkyl, hydroxyl, alkoxy, amino, alkylamino, dialkylamino and halogen,

or a pharmaceutically acceptable salt thereof;
or

b11) (1R, 2S, 5R) 2-(aminocarbonyl)-7-oxo-1,6-diazabicyclo[3.2.1]octane-6-sulfonic acid or a diazabicyclooctane derivative of the general formula XIII:



XIII

in which

R23 signifies hydrogen, carboxylic acid, alkoxycarbonyl or carboxamide which may be substituted, and
R24 signifies SO_3H, OSO_3H or OCRjRj'COOH, wherein Rj and Rj' are as defined for formula II,

or a pharmaceutically acceptable salt thereof.

[0010] As a preferred embodiment of the invention, pharmaceutical compositions may comprise the monobactam antibiotic and two or more β-lactamase inhibitors selected from one of the formulae II to XIII of b1) to b11), these two or more compounds being different from each other.

Detailed description of the invention

[0011] It has surprisingly been found that the efficacy of monobactam antibiotics of claim 1 against aerobic Gram-negative bacteria can be potentiated by co-using a β-lactamase inhibitor according to any one of the formulae II to XIII.
[0012] In claim 1, when the oxoazetidine ring is lying in the plane of the paper, R3 points downwards from the plane, and R2 points upwards from the plane.
[0013] For the purposes of the present invention, the β-lactamase inhibitors of the above formula III are not considered as antibiotically active compounds in the sense of claim 1. The compounds of claim 1 have the oximino group predominantly the "syn" configuration shown in the formula, whereas the β-lactamase inhibitors III have the oximino group specifically in the "anti" configuration shown in formula III.
[0014] The term "alkyl", as used in the present application, preferably means straight-chain or branched (C_1-C_7)alkyl such as in particular methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, isopropyl, isobutyl, tert-butyl or neopentyl.

[0015] The term "alkoxy", as used in the present application, preferably means straight-chain or branched (C_1-C_7) alkoxy, such as in particular methoxy, ethoxy, propoxy, 1- or 2-butoxy, 1-, 2-, or 3-pentyloxy, 1-, 2- or 3-hexyloxy, 1-, 2-, 3-, or 4-heptyloxy or tert-butoxy. The term "alkylhydroxyl" as also used, shall be considered synonymous to "alkoxy"; in particular for the alkyl in "alkylhydroxyl" the same definition shall apply as given above for "alkyl".

[0016] The term "carboxamide which may be substituted" preferably has the meaning that the carboxamide has 0 to 2 hydrogen atoms attached to the amino moiety, with the remainder of the substituents on the amino moiety being alkyl or phenyl which may be substituted.

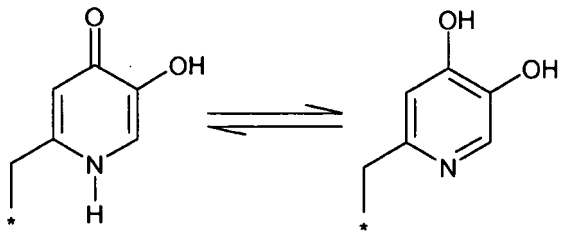
[0017] The term "imine which may be substituted" preferably means that the imine bears at the imine nitrogen hydrogen, alkyl, phenyl which may be substituted or benzyl which may be substituted.

[0018] The terms "optionally substituted phenyl" and "optionally substituted benzyl", if given without specifically indicated substituents, shall preferably mean that the phenyl or benzyl is optionally substituted with 1 to 5 substituents selected from alkyl, alkoxy, dialkylamino and halogen, wherein the "alkyl" itself and the alkyl in dialkylamino and alkoxy has the meaning as defined above.

[0019] The term "linear spacer", as used in the present application, preferably means a linear divalent group selected from -O-, -S-, -NH-, -NH-NH -, -CH_2-, -CO-, -CH_2O-, -CHb_2CH_2-, -CH=CH-, -CH_2NH-, -S-CH_2-, -SO_2-, -CH_2-, -O-CH_2-, -S-CH_2CH_2-, - CH_2CH_2-NH-, -CH_2-NH-CO-CH_2CH_2-, -CH_2-NH-CO-O-CH_2CH_2, -CH_2-NH-CO-NH-CH_2CH_2, -CH_2-O-CO-NH-CH_2CH_2-, -CH(OH)-, -CH(COOH)-, - $CH(OSO_3H)$-, -$CH(OCONH_2)$- and -CH [$CH(CH_3)_2$]-.

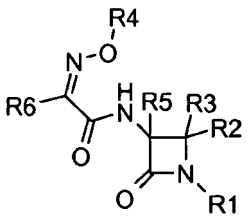
[0020] The compounds of claim 1 contain an acidic group (R1 is SO_3H) and may be present as a salt with a pharmaceutically acceptable inorganic base (e.g. NaOH, KOH, NH_3, K_2CO_3, Na_2CO_3, Na_2HPO_4 or K_2HPO_4) or organic base (e.g. NEt_3, $HNiPr_2$, triethanolamine, TRIS or basic amino acids such as arginine and lysine). The use of such salts of compounds of claim 1 is encompassed by the invention. The compounds of claim 1 contain both an acidic group (R1 is SO_3H) and a basic group (4-aminopyrimidin-2-yl) and may form an inner, zwitterionic salt; such inner salts are also intended to be encompassed by the claims.

[0021] R4 contains a 4-pyridone moiety, wherein Rd is selected from hydrogen and hydroxy, and there is the possibility of tautomerism:



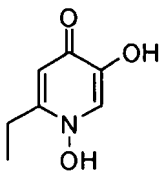
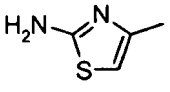
[0022] The invention intends to encompass the use of any such tautomers.

[0023] Examples of compounds for combinations are according to the following formula I and table 1 (R5 is in these compounds always H):

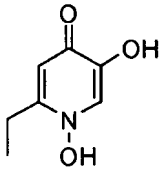
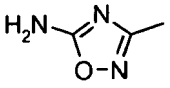
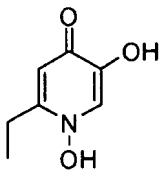
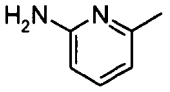
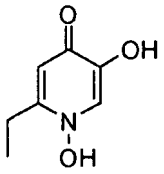
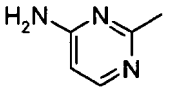


I

table 1

Compound number	R1	R2	R3	R4	R6
1	SO_3H	H	CH_3		

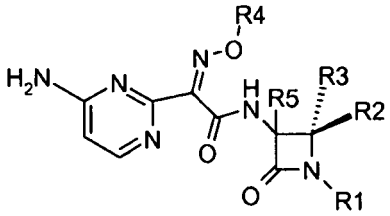
(continued)

Compound number	R1	R2	R3	R4	R6
16	SO_3H	H	CH_3		
20	SO_3H	H	CH_3		
21	SO_3H	H	CH_3		

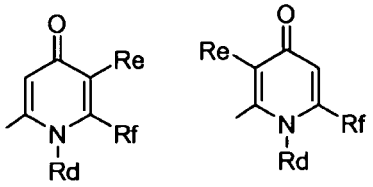
[0024] The numbering of the compounds as given in above table 1 is used in the following for the sake of conciseness.

[0025] The compound of the above table 1 with compound number underscored and bold is part of the present invention.

[0026] The compounds of the invention are those of the following formula Ib:



and the pharmaceutically acceptable salts thereof, wherein the residues R1, R2, R3, R4 and R5 are as defined in claim 1. In these compounds R1 is SO_3H, R2 is H, R3 is methyl and R4 is C(Rx)(Ry)Z; whereby Rx = Ry = H, and Z is a group of one of the formulae



wherein Rd, Re and Rf are individually selected from hydrogen and hydroxy, with the proviso that at least two of Rd, Re and Rf are hydroxy (most preferably Rd and Re are hydroxy and Rf is hydrogen).

[0027] The antibiotically active monobactams of claim 1 may firstly be combined with

b1) β-lactamase inhibitors of the above general formula II.

[0028] In formula II, R8 is preferably of the formula Q-$(X)_r$-CO-. The following subgroups are more preferable within this formula:

a) With X = -CH_2- and r = 1; wherein Q is a pyridinium group which may be substituted with one to three substituents, preferably one to two substituents, selected from alkyl; perfluoroalkyl, in particular trifluoromethyl; phenyl; benzyl; R_uR_vN-, wherein R_u and R_v are independently selected from hydrogen, alkyl, cycloalkyl, pyrrolidinyl, carbamoyl and

N-(carbamoylalkyl)carbamoyl, or wherein R_u and R_v taken together form an alkylene bridge -(CH_2)-$_w$, with w being an integer number of 3 to 6; alkylcarbonyl; R_uR_vNCO-, wherein R_u and R_v are as defined before; (alkoxycarbonyl) alkyl; thiocarbamoyl and alkoxycarbonyl; or wherein Q is a pyridinium group which is fused with a 5-6 membered carbocycle; and thioamide. Examples within this subgroup are pyridinium, 2-, 3- or 4-aminopyridinium, 3-N-methylaminopyridinium, 3-N,N-dimethylaminopyridinium, 4-(N-methylamino)pyridinium, 4-(N,N-dimethylamino)pyridinium, 3-carbamoylpyridinium, 3-(N-methylcarbamoyl)pyridinium, 3-(N,N-dimethylcarbamoyl)pyridinium, 4-carbamoylpyridinium, 4-(N-methylcarbamoyl)pyridinium, 4-(N,N-dimethylcarbamoyl)pyridinium, 3-(N-cyclopropylcarbamoyl)pyridinium, 4-(N-cylopropylcarbamoyl)pyridinium, 4-(N-methylcarbamoyl)pyridinium, 3-(methoxycarbonyl) pyridinium, 3-(ethoxycarbonyl)pyridinium, 4-(methoxycarbonyl)pyridinium, 4-(ethoxycarbonyl)pyridinium, 3-thiocarbamoylpyridinium, 3-(N-methylthiocarbamoyl)pyridinium, 3-(N,N-dimethylthiocarbamoyl)pyridinium, 4-thiocarbamoylpyridinium, 4-(N-methyl-thiocarbamoyl)pyridinium, 4-(N,N-dimethylthiocarbamoyl)pyridinium, 2, 3-, 2, 4-, 2, 5-, 2,6-, 3,4-, 3,5-, 3,6-dimethylpyridinium, 3- or 4-isopropylpyridinium, 3- or 4-(trifloromethyl)pyridinium, 3- or 4-phenylpyridinium, 3- or 4-benzylpyridinium, quinolinium, isoquinolinium, 5,6,7,8-tetrahydroquinolinium and 5,6,7,8-tetrahydroisoquinolinium. In this subgroup, R7 is preferably -SO_3^- or -OSO_3^-, to form a pharmaceutically acceptable inner salt. The compounds II of this subgroup a) themselves are per se also part of the invention, but compound 102 of table 2 below is known from J. Med. Chem. 1998, 41(21), 3961, and does per se not form part of the invention.

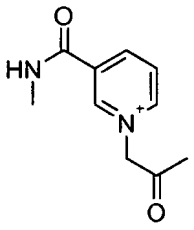
b) With X = -SCH_2- and r = 1; wherein Q is 1,2,3,4-tetrazol-5-yl, which may be substituted at its 1-position with a substituent selected from alkyl, aminoalkyl or alkoxyalkyl. Examples for this substituent are methyl, ethyl, propyl, butyl, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(N,N-dimethylamino)ethyl, 3-aminopropyl, 3-(N-methylamino)propyl, 3-(N,N-dimethylamino)propyl, 2-(N-ethylamino)ethyl, 2-(N,N-diethylamino)ethyl, 3-(N-ethylamino)propyl and 3-(N, N-diethylamino)propyl. In these compounds, R7 is preferably -SO_3H or OSO_3H, whereby the possibility of formation of an inner, acid addition salt may be allowed, to form a pharmaceutically acceptable inner salt.

c) With X = -CH_2NH_2- and r = 1; wherein Q is phenyl which may be substituted with one to two substituents selected from hydroxy and alkoxy, or a 5-6-membered heterocycle which preferably is selected from oxazol-2-yl, -3-yl or -4-yl, furan-2-yl or 3-yl, thiophen-2-yl or -3-yl, 1,3-thiazol-2-yl, -3-yl, -4-yl or -5-yl and which optionally may be substituted with one to two substituents selected from alkyl and alkoxy.

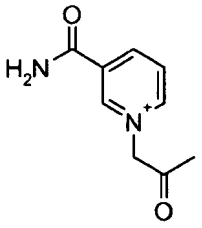
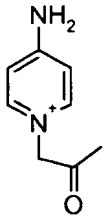
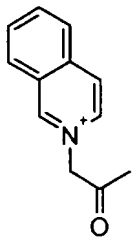
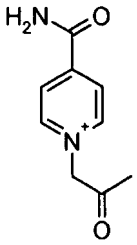
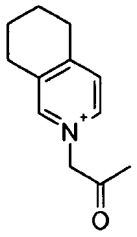
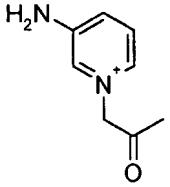
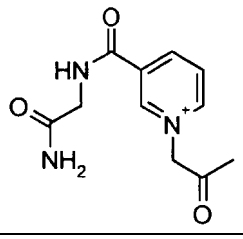
d) With X = -NH_2- and r = 1, wherein Q is phenyl which may be substituted with one to two substituents selected from hydroxy; alkoxy and a substitued urea of the formula $H_2N[(CH_2)_mO]_n(CH_2)_oHNCONH$- or a substituted carbamate of the formula $H_2N[(CH_2)_mO]_n(CH_2)_oHNCOO$-, wherein m and o are independently integer numbers from 2 to 3 and n is an integer number from 0 to 1. Examples for Q here are phenyl, 2-, 3-and 4-hydroxyphenyl, 2,3-, 2,4-, 2,6-, 3,4-, 3,5- and 3,6-dihydroxyphenyl, 2-, 3- and 4-methoxyphenyl, 3-[N'-{2-(2-amino-ethoxy)et-hyl}carbamoylamino]phenyl, 3-[N'-{2-(3-aminopro-poxy)et-hyl}carbamoylamino]phenyl, 3-[N'-{3-(2-aminoeth-oxy)propyl} carbamoylamino]phenyl, 3-[N'-{3-(3-aminopro-poxy)propyl}carbamoylamino]phenyl, 4-[N'-{2-(2-aminoeth-oxy) ethyl}carbamoylamino]phenyl, 4-[N'-{2-(3-aminopro-poxy)ethyl}carbamoylamino]phenyl, 4-[N'-{3-(2-aminoeth-oxy) propyl}carbamoylamino]phenyl, 4-[N'-{3-(3-aminopro-poxy)propyl}carbamoylamino]phenyl, 3-[N'-{2-(2-aminoethoxy)et-hyl}carbamoyloxy]phenyl, 3-[N'-{2-(3-aminopropoxy)ethyl}carbamoyloxy]phenyl, 3-[N'-{3-(2-aminoethoxy)propyl}carbamoyloxy]phenyl, 3-[N'-{3-(3-aminopropoxy)propyl}carbamoyloxy]phenyl, 4-[N'-{2-(2-aminoethoxy)ethyl}carbamoyloxy]phenyl, 4-[N'-{2-(3-aminopropoxy)ethyl}carbamoyloxy]phenyl, 4-[N'-{3-(2-aminoethoxy)propyl}carbamoyloxy]phenyl and 4-[N'-{3-(3-aminopropoxy)propyl}carbamoyloxy]phenyl.

[0029] Particularly preferred examples of the compounds of formula II are according to the following table 2

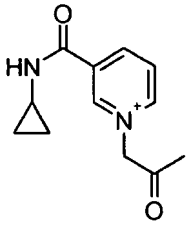
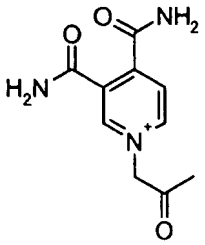
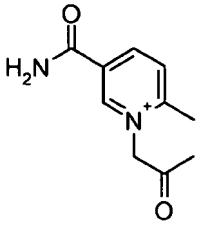
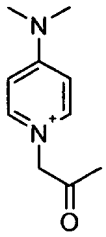
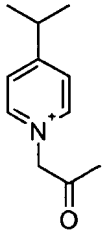
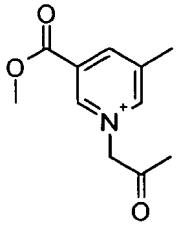
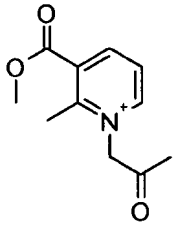
table 2

Compound number	R7	R8
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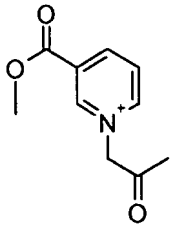
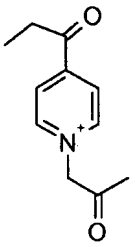
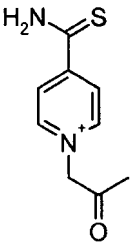
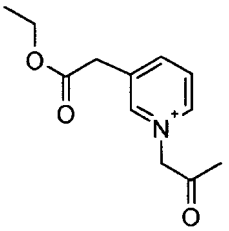
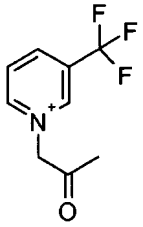
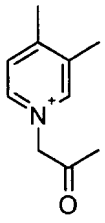
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Compound number	R7	R8
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104	SO_3^-	
105	SO_3^-	
106	SO_3^-	
107	SO_3^-	
108	SO_3^-	

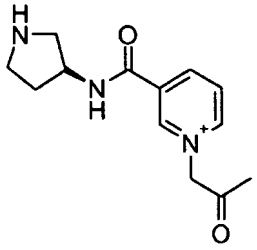
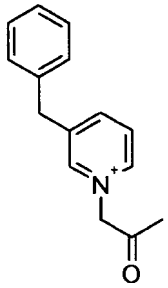
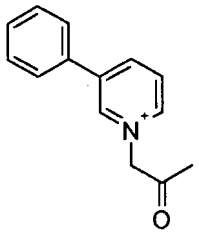
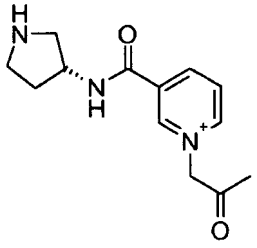
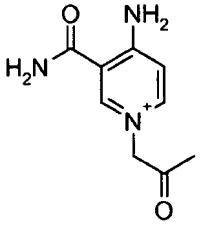
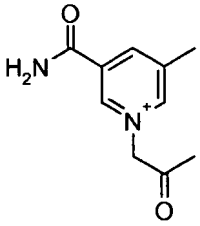
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Compound number	R7	R8
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110	SO_3^-	
111	SO_3^-	
112	SO_3^-	
113	SO_3^-	
114	SO_3^-	
115	SO_3^-	

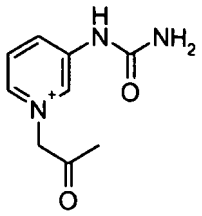
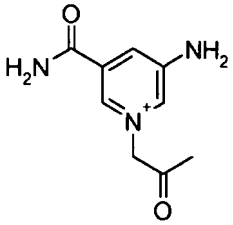
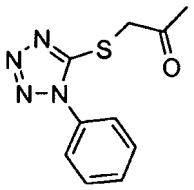
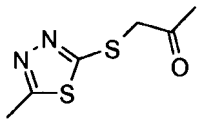
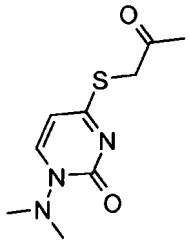
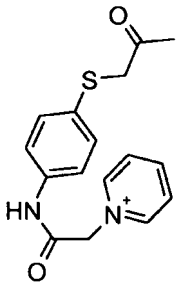
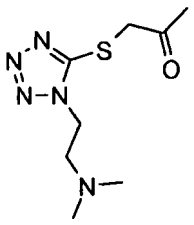
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Compound number	R7	R8
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118	SO_3^-	
119	SO_3^-	
120	SO_3^-	
121	SO_3^-	

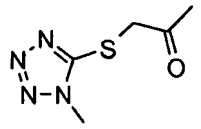
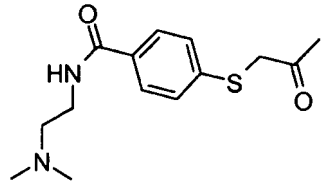
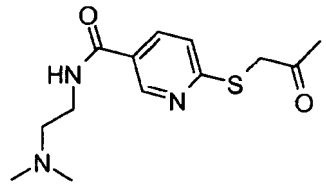
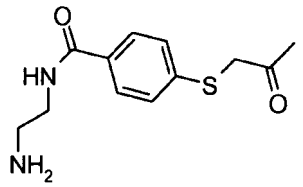
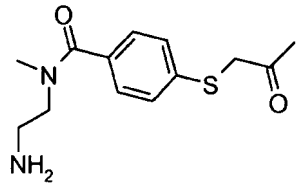
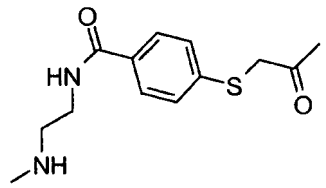
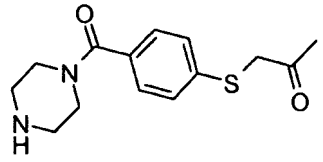
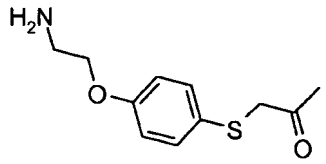
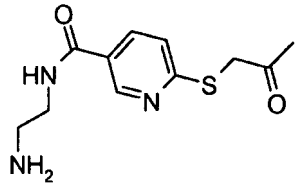
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Compound number	R7	R8
122	SO_3^-	
123	SO_3^-	
124	SO_3^-	
125	SO_3^-	
126	SO_3^-	
127	SO_3^-	

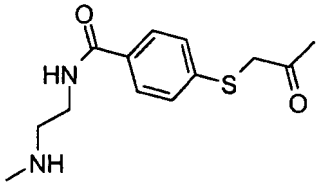
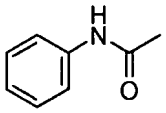
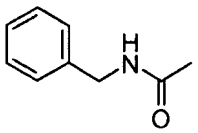
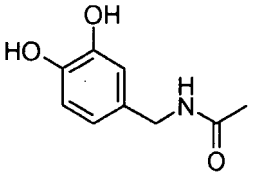
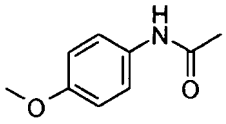
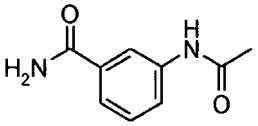
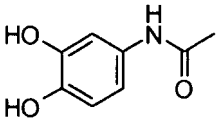
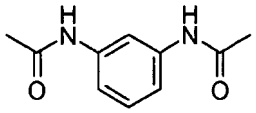
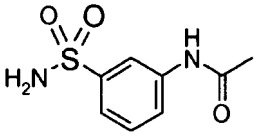
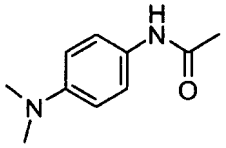
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Compound number	R7	R8
128	SO_3^-	
129	SO_3^-	
201	SO_3Na	
202	SO_3Na	
203	SO_3H	
204	SO_3^-	
205	SO_3H	

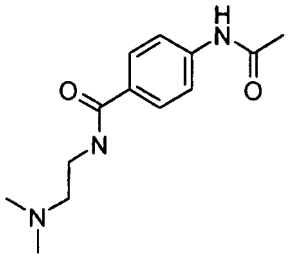
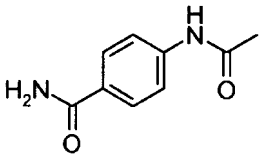
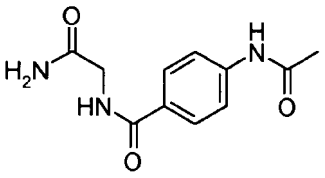
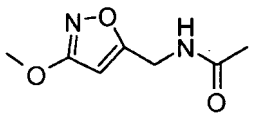
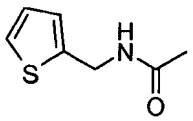
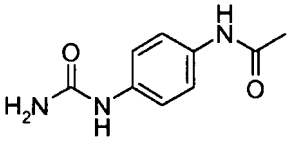
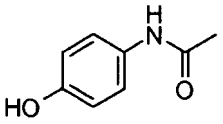
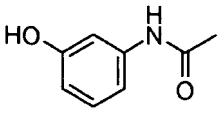
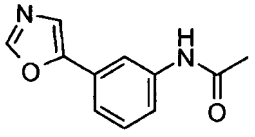
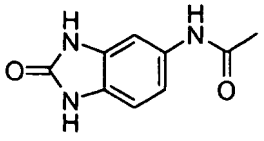
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Compound number	R7	R8
206	SO_3Na	
207	SO_3H	
208	SO_3H	
209	SO_3H	
210	SO_3H	
211	SO_3H	
212	SO_3H	
213	SO_3H	
214	SO_3H	

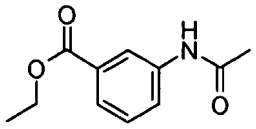
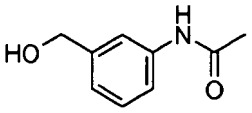
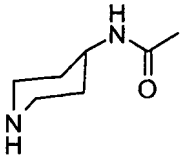
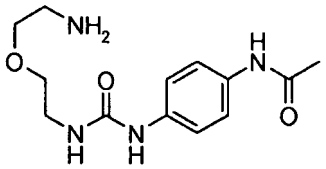
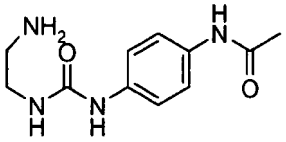
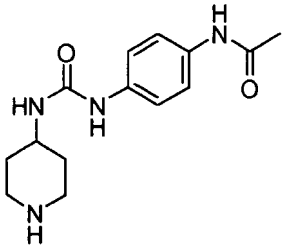
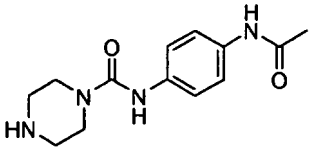
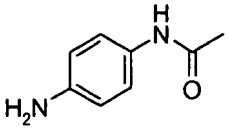
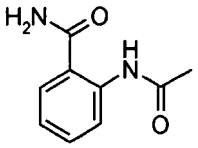
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Compound number	R7	R8
215	SO_3H	
301	SO_3Na	
302	SO_3Na	
303	SO_3Na	
304	SO_3Na	
305	SO_3Na	
306	SO_3Na	
307	SO_3Na	
308	SO_3Na	
309	SO_3Na	

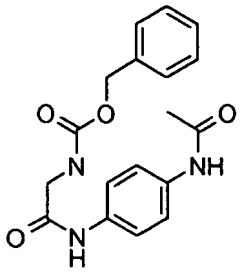
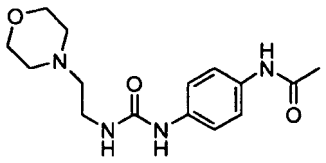
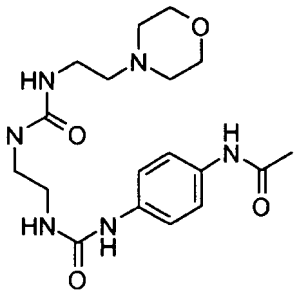
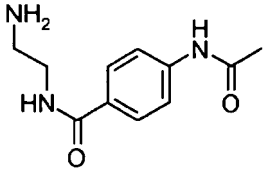
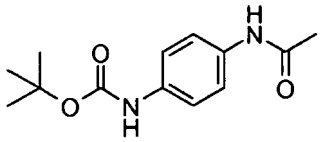
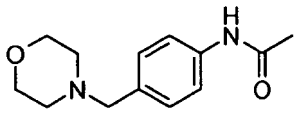
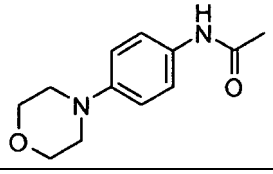
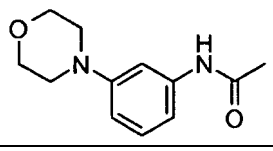
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Compound number	R7	R8
310	SO_3Na	
311	SO_3Na	
312	SO_3Na	
313	SO_3Na	
314	SO_3Na	
315	SO_3Na	
316	SO_3Na	
317	SO_3Na	
318	SO_3H	
319	SO_3Na	

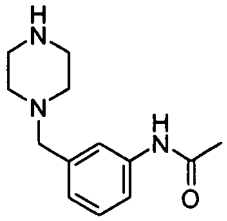
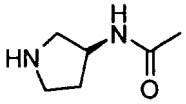
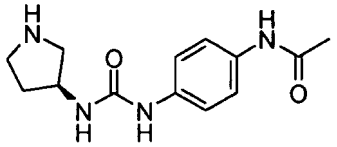
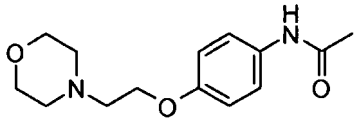
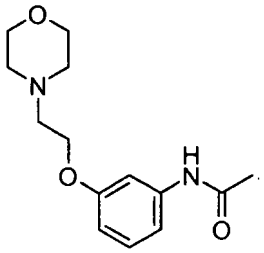
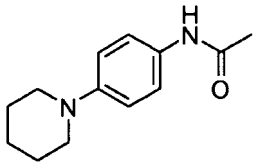
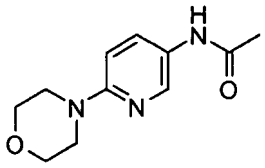
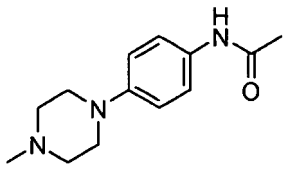
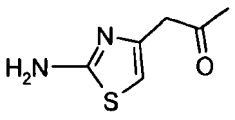
(continued)

Compound number	R7	R8
320	SO_3Na	
321	SO_3Na	
322	SO_3H	
323	SO_3H	
324	SO_3H	
325	SO_3H	
326	SO_3H	
327	SO_3Na	
328	SO_3Na	

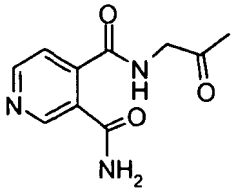
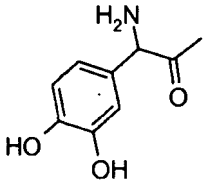
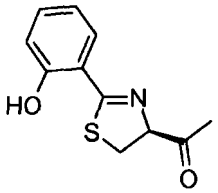
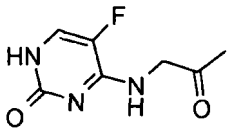
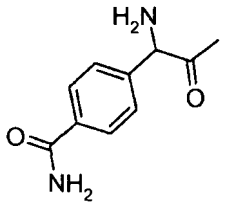
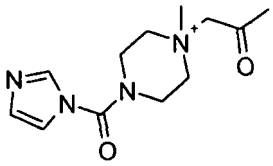
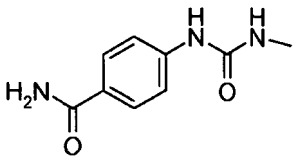
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Compound number	R7	R8
329	SO_3Na	
330	SO_3H	
331	SO_3H	
332	SO_3H	
333	SO_3Na	
334	SO_3H	
335	SO_3H	
336	SO_3H	

(continued)

Compound number	R7	R8
337	SO_3H	
338	SO_3H	
339	SO_3H	
340	SO_3H	
341	SO_3H	
342	SO_3H	
343	SO_3H	
344	SO_3H	
401	SO_3H	

(continued)

Compound number	R7	R8
402	SO_3H	
403	SO_3H	
404	SO_3Na	
405	SO_3Na	
406	SO_3H	
407	SO_3^-	
408	SO_3Na	

[0030] The numbering of the preferred compounds of formula II as given in above table 2 is used in the following for the sake of conciseness.

[0031] The compounds of the above table 2 are, when their compound numbers are underscored and bold, part of the invention of WO 2007/065288. Otherwise they are disclosed in EP-A-0-508 234, US-B-6,566,355 and J. Med. Chem. 1998, 3961. These publications are hereby incorporated by reference.

[0032] The compounds of claim 1 may also be combined with other β-lactamase inhibitors. These further inhibitors are:

b2) monobactam derivatives of the above general formula III:

Examples of these compounds are disclosed in WO-A-99/10324 and WO-A-98/47895, incorporated herein by reference. A preferred example of these compounds is 3-{(2E)-3-[(1,5-dihydroxy-4-oxo(2-hydropyridyl))methoxy]-2-(2-thienyl)-3-azaprop-2-enoylamino}(3S,4S)-4-methyl-2-oxoazetidinesulfonic acid disclosed in WO-A-98/47895.

b3) penam sulfone derivatives of the above general formulae IV and V:

Here, preferred examples of the 5-6 membered heteroaromatic ring as R12 are 1,3-thiazol-2-yl, 1,2,4-oxadiazol-3-yl and 1,2,3-triazol-1-yl.

Particularly preferred examples of the compounds of formula V are sulbactam, tazobactam and the compounds of the following table (in parentheses the source):

R10	R11	Compound number
hydrogen	(1Z)-2-cyanovinyl	501 EP-A-0 640 607
hydrogen	(1E)-3-oxo-but-1-en-1-yl	502 EP-A-0 640 607
hydrogen	(1Z)-2-(1,3-thiazol-2-yl)vinyl	503 EP-A-0 640 607
hydrogen	(1E)-2-(1,2,4-oxadiazol-3-yl)vinyl	504 EP-A-0 640 607
carboxymethylene	CH_3	(Bioorg. Med. Chem. Lett. 1995, 1513)
hydrogen	(1E)-2-methoxy-2-azavinyl	US-A-5, 686, 441
hydrogen	(1E)-2,3-diaza-4-oxo-pent-1-en-1-yl	US-A-5,686,441

The numbers used in the rightmost column of this table are also used in the tests for biological activity (see below).

b4) oxapenam derivatives of the above general formula VI:

A preferred compound of formula VI is clavulanic acid or a customary pharmaceutically acceptable salt thereof (i.e. a clavulanate).

b5) penem derivatives of the above general formula VII:

Here, preferred examples of the 5-6 membered heteroaromatic ring which may be bound over a -CH=CH- spacer as R15 are 1,2,3-triazol-4-yl, 2H,3H-imidazo[2,1-b]1,3-thiazolidin-6-yl and 2'-[1-methyl-1,2,3-triazolin-4-yl]vinylidene.

Preferred examples for inhibitors of formula VII are e.g. 6-[(1-methyl(1,2,3-triazol-4-yl))methylene]-5-oxo-6aH-azetidino [2,1-b]1,3-thiazoline-3-carboxylic acid and 6-(2H,3H-imidazo[2,1-b]1,3-thiazolidin-6-ylmethylene)-5-oxo-6aH-azetidino [2,1-b]1,3-thiazoline-3-carboxylic acid (as described in Antimicrob. Agents Chemother. 1989, 1580 and Antimicrob. Agents Chemother. 1991, 1748), and 6-[(2E)-3-(1-methyl(1,2,3-triazolin-4-yl))prop-2-enylidene]-5-oxo-6aH-azetidino [2,1-b]1,3-thiazoline-3-carboxylic acid (as described in J. Antibiotic 1997, 50, 350).

b6) cephem sulfone derivatives of the above general formula VIII:

Here, a preferred example of the 5-6 membered heteroaromatic ring as R16 is 2-thienyl.

Preferred examples are here 3-(acetyloxymethyl)-1,1,6-trioxo-7-(2-pyridylmethylene)-2H,7aH-azetidino[2,1-b]1,3-thiazine-4-carboxylic acid (Biorg. Med. Chem. Lett. 2000, 853 and Biorg. Med. Chem. Lett. 2000, 847) and 3-(acetyloxymethyl)-7-{[(tert-butyl)oxycarbonyl]methylene}-1,1,6-trioxo-2H,7aH-azetidino[2,1-b]1,3-thiazine-4-carboxylic acid (J. Med. Chem. 1995, 38, 1022).

b7) meropenem, ertapenem, doripenem or a carbapenem derivative of the above general formula IX:

Here, preferred combinations for Rk and R1 are: Rk = hydrogen and R1 = sulfamoyl or 3-carboxyphenyl (or vice versa); and Rk = R1 = methyl.

Preferred examples are imipenem, meropenem, ertapenem and doripenem.

b8) boronate derivatives of the above general formula X.

b9) boronate derivatives of the above general formula XI:

Examples of these compounds are 3-[(4-phenylsulfonyl-2-thienylsulfonyl)amino]phenyl]boronic acid (Chem. Biol. 2001, 8, 593) and [3-[[4-[(4-carboxyphenylsulfonyl)amino]phenylsulfonyl]amino]phenyl]boronic acid (Chem. Biol. 2001, 8, 594).

b10) phosphonate derivatives of the above general formula XII

Preferred examples of these are {[(4-nitrophenoxy)(hydroxyphosphoryl)]methyl}[benzylsulfonyl]amine, {[(4-nitrophenoxy)(hydroxyphosphoryl)]methyl}(phenylsulfonyl)amineand {[(4-nitrophenoxy)(hydroxyphosphoryl)]methyl}(2-thienylsulfonyl)amine, (benzo[b]thiophen-2-ylsulfonyl){[(4-nitrophenoxy)(hydroxyphosphoryl)]methyl}amine and 2-[(4-nitrophenoxy)(hydroxyphosphoryl)]-1-(phenylsulfonyl)hydrazine (all described in US-A-2004/082546 and US-A-2004/029836); and

b11) diazabicyclooctane derivatives of the above general formula XIII or (1R, 2S, 5R) 2-(aminocarbonyl)-7-oxo-1,6-diazabicyclo[3.2.1]octane-6-sulfonic acid (as described in WO-A-2002/01219, WO-A-2002/010172, FR-A-2835186 and FR-A-2848210).

[0033] Pharmaceutical compositions may comprise, besides the compound of claim 1, two or more β-lactamase inhibitors selected from the above formulae II to XIII, being different from each other. Pharmaceutical compositions comprising triple combinations of a compound of claim 1 and two different β-lactamase inhibitors selected from the groups b1) to b11) are preferred.

[0034] More preferred are composition wherein the above double combinations are further combined with one of

sulbactam, clavulanic acid or a customary pharmaceutically acceptable salt thereof, i.e. a clavulanate. These compositions thus comprise triple combinations.

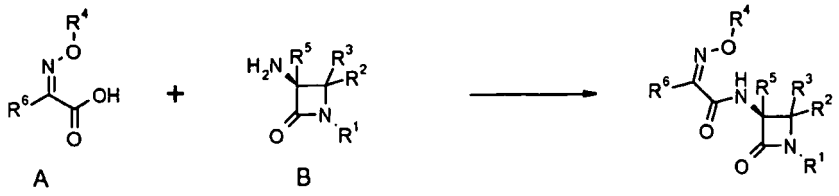
[0035] Particularly preferred are compositions with the following triple combinations (the numbers are as in the foregoing tables 1 and 2):

Compound 21	Compound 102	Sulbactam
Compound 21	Compound 102	Clavulanate
Compound 21	Compound 323	Sulbactam
Compound 21	Compound 323	Clavulanate
Compound 21	Compound 324	Sulbactam

[0036] The compounds of claim 1 can be made as described in the following.

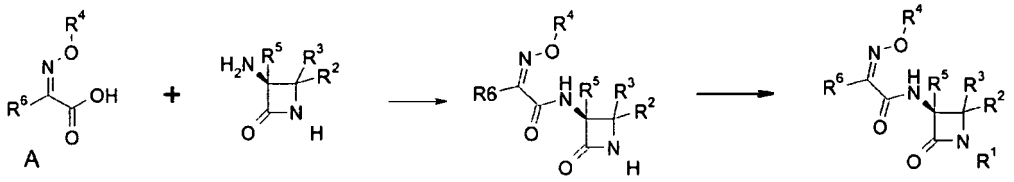
[0037] The compounds of claim 1 can generally be prepared by reacting heteroaryl carboxylic acids of general formula A with the 3-amino-azetidin-2-one compound of formula B (scheme 1). In this scheme, R4 may also have the meaning of a protecting group, which may then be removed, in order to subsequently connect the actually desired R4.

Scheme 1



[0038] The coupling reaction of compounds of general formula A with the compound of formula B can be performed with the corresponding acyl chlorides of the heteroaryl carboxylic acids of general formula A or with the carboxylic acids A themselves and DCC (Chem. Pharm. Bull 1983, 2200) or with an activated ester of the aryl or heteroaryl carboxylic acids of general formula A, such as the N-hydroxysuccinimidyl ester (see Org. Process Res.& Dev. 2002, 863) or the benzothiazolyl thioester (see J. Antibiotics 2000, 1071). Alternatively, compounds of claim 1 can also be prepared as outlined in scheme 2 (R1 = SO_3H; see also J. Antibiotics 1985, 346).

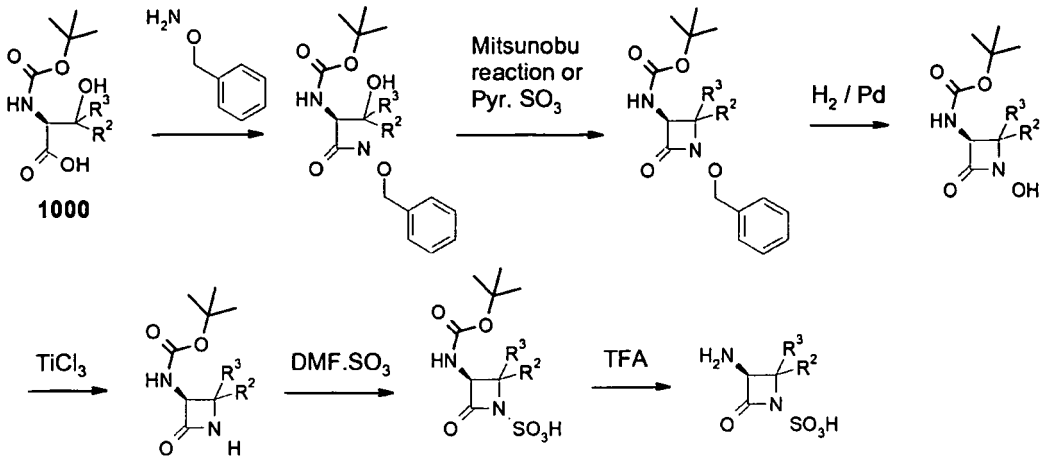
Scheme 2



A) Preparation of the compound B

[0039] The preparation of the compound of formula B can be carried out in different ways (Scheme 3). (J. Org. Chem. 1980, 410; J. Antibiotics 1986, 76; J. Med. Chem. 1985, 1447).

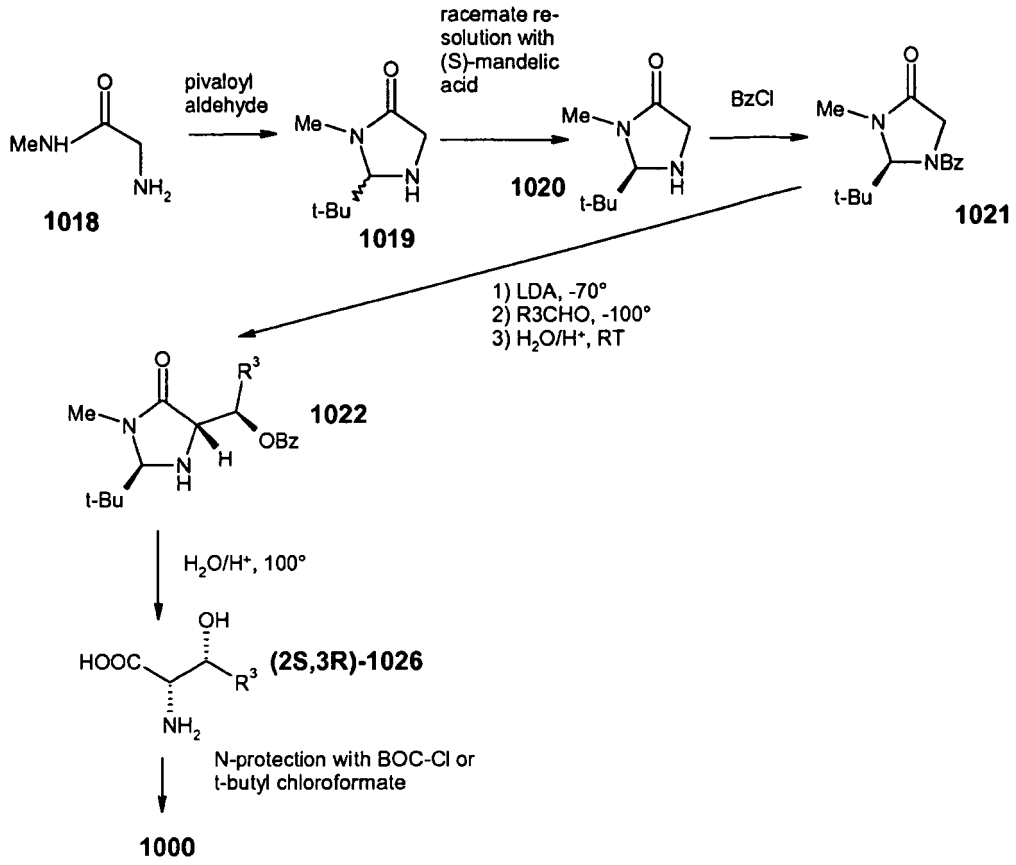
Scheme 3



[0040] A-1) In the above scheme 3, an enantiomerically pure N-protected β-hydroxy amino acid **1000** is required as the starting material. This precursor **1000** can be prepared as outlined in the following section A-1-III):

[0041] A-1-III) R^2 is H and R^3 is alkyl. A synthesis according to following scheme A-1-III) may be adopted to form **1000:**

Scheme A-1-III

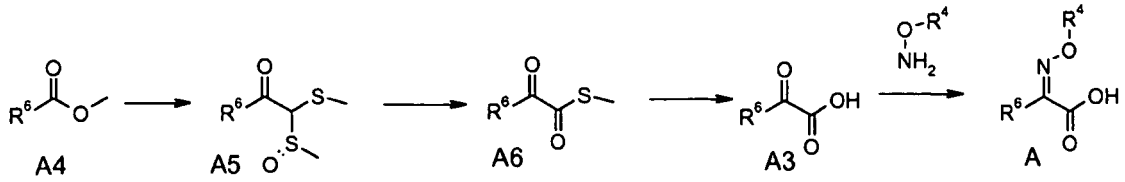


[0042] This methodology was developed by Seebach (Helv. Chim. Acta 1987. 237). In scheme A-1-III, the conversions yield the N-protected β-hydroxy amino acid **1000** where R^2 = hydrogen, in defined configuration.

B) Preparation of compounds A

[0043] The preparation of compounds of general formula A required in schemes 1 and 2 can be carried out in a customary way by reacting an appropriately R6-substituted keto acid A3 with an appropriately R4-etherified hydroxylamine (scheme 7 below)

Scheme 7



[0044] The R6-substituted keto acid A3 required in scheme 7 can be prepared as described in the following.

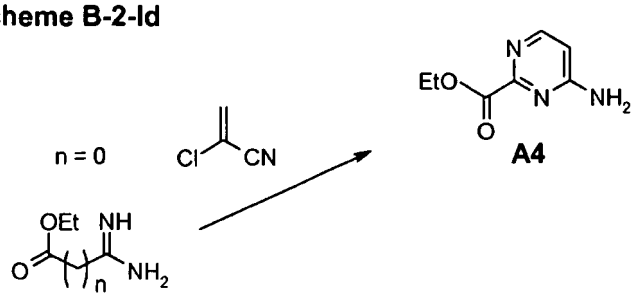
[0045] The R6-substituted keto acid A3 can be prepared via the condensation of methyl methylthiomethyl sulfoxide according to above scheme 7 (J. Antibiotics, 1984, 546, J. Antibiotics, 1984, 557) in a 4 step synthesis from the esters A4 $R6COOCH_3$ or R6COOEt. The methyl methylthiomethylsulfoxide is first condensed with A4 derivatives to give the methyl thioglyoxylate compound A6 after acidic treatment.

[0046] Preparation of intermediate A4 (scheme 7) is as outlined in the following subsection B-2-Id).

[0047] B-2-Id) R6 is a pyrimidine derivative.

Scheme B-2-Id (below) shows that amidine derivatives can lead to 2-substituted pyrimidine A4 (DE-OS-2848912, J. Antibiotics 1984, 546).

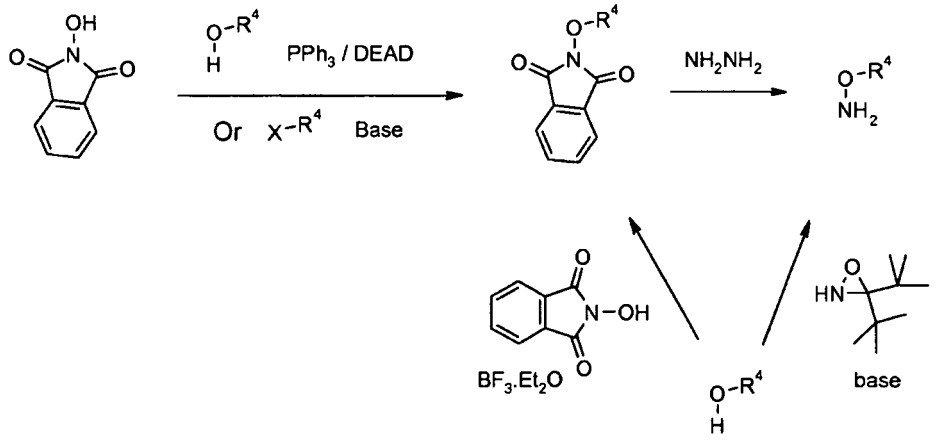
Scheme B-2-Id



[0048] B-3) The hydroxylamines required in above scheme 7, can be prepared in several methods, as outlined in scheme 8 below.

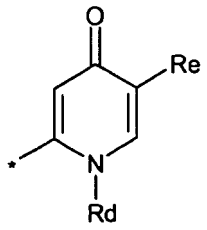
[0049] These hydroxylamines may be prepared firstly according to J. Antibiotics, 2000, 1072 with N-hydroxyphthalimide via Mitsunobu reaction conditions in presence of the alcohols R4-OH or by alkylation of N-hydroxyphthalimide in presence of activated compounds R4-X (X can be halogens like Cl, Br, I, or activated sulfonate esters like mesylate, tosylate, triflate, etc.). Formation of the final hydroxylamines may be performed in presence of either hydrazine or methyl hydrazine. The oxaziridine technology developed by Ellman can also been employed to give directly deprotected O-substituted hydroxylamines (J. Org. Chem. 1999, 6528). (scheme 8).

Scheme 8



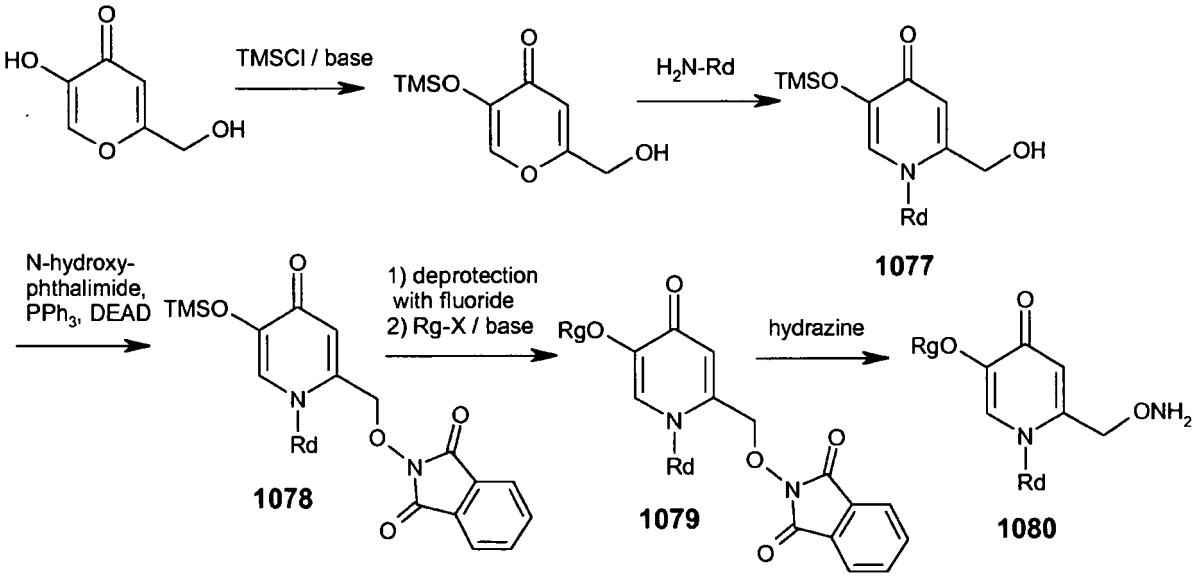
[0050] Alcohols R4-OH or compounds R4-X are either commercially available or may be prepared as described in following section B-3-Id).

[0051] B-3-Id) For hydroxylamines where in R4 Z is



wherein Re and Rd are ORg (Rg being hydrogen for each Re and Rd); and wherein Rx = Ry = H; the following synthetic scheme B-3-Id may be adopted:

Scheme B-3-Id



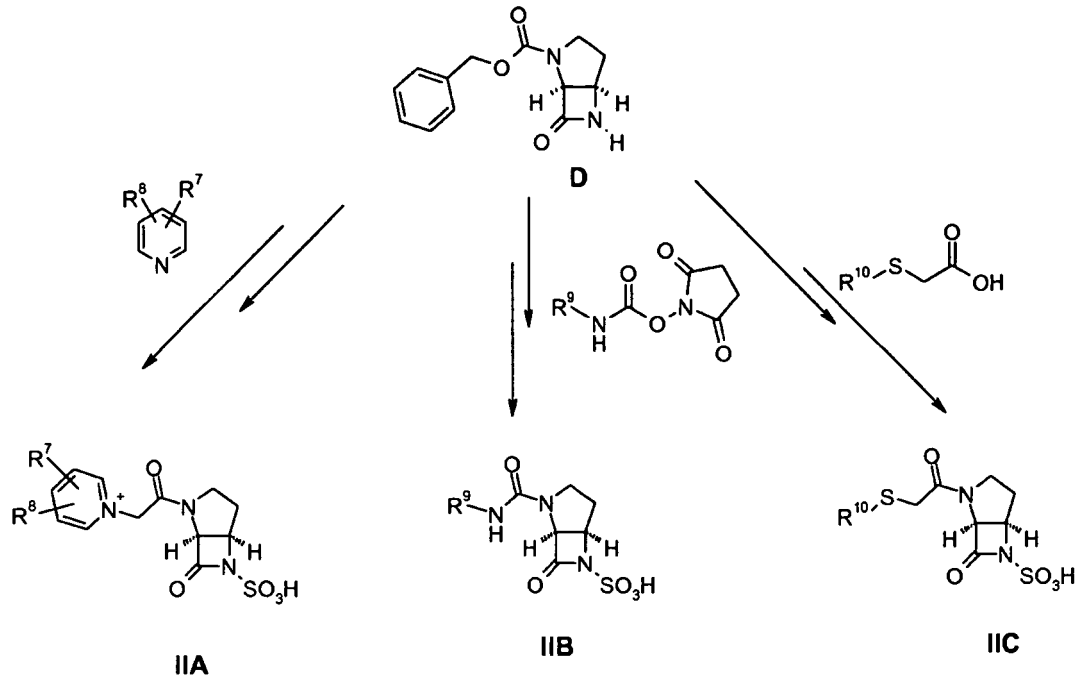
[0052] This scheme adheres to the synthetic procedure described in EP-A-0 251 299. The kojic acid used as the starting material is commercially available. In the conversion from the silylprotected kojic acid to **1077** the reactands H_2N-Rd are amines, when Rd is hydrogen, alkyl or optionally substituted benzyl, they are hydrazines, when Rd is amino or monoalkylamino; they are carbamates, when Rd is alkoxycarbonyl; and when Rd is ORg, these reactands are hydroxylamines. In the conversion of **1078** to **1079**, the reactands Rg-X are hydrogen halides, alkyl halides or benzyl halides, wherein X is preferably Br or I. These reactands Rg-X are known or easily made from the corresponding alcohols Rg-OH. In the above scheme, instead of trimethylsilyl other protecting groups could also be used, such as benzyl, diphenyl or trityl as reported in J. Antibiotics 1990, 1450.

[0053] After formation of the ketoacid derivative A3, the condensation with O-substituted hydroxylamine (prepared or commercially available like O-methyl hydroxylamine) may be performed to lead to compounds of general formula A. The condensation of the hydroxylamines R4-ONH_2 with the keto acid derivatives A3 to form the compounds A may then follow the procedure described in J. Antibiotics 2000, 1071 and WO-A-02/22613.

[0054] The β-lactamase inhibitors of formula II are compounds known from the above cited literature references (EP-A-0 508 284 and US-B-6,566,355) or can be made in an analogous manner or can be made as described in the following scheme 10.

[0055] The intermediate compound D (J. Med. Chem. 1998, 3961 and EP-A-0 508 234) gives access to compounds of formula IIA, IIB or to IIC using different synthetic routes outlined in scheme 10.

Scheme 10

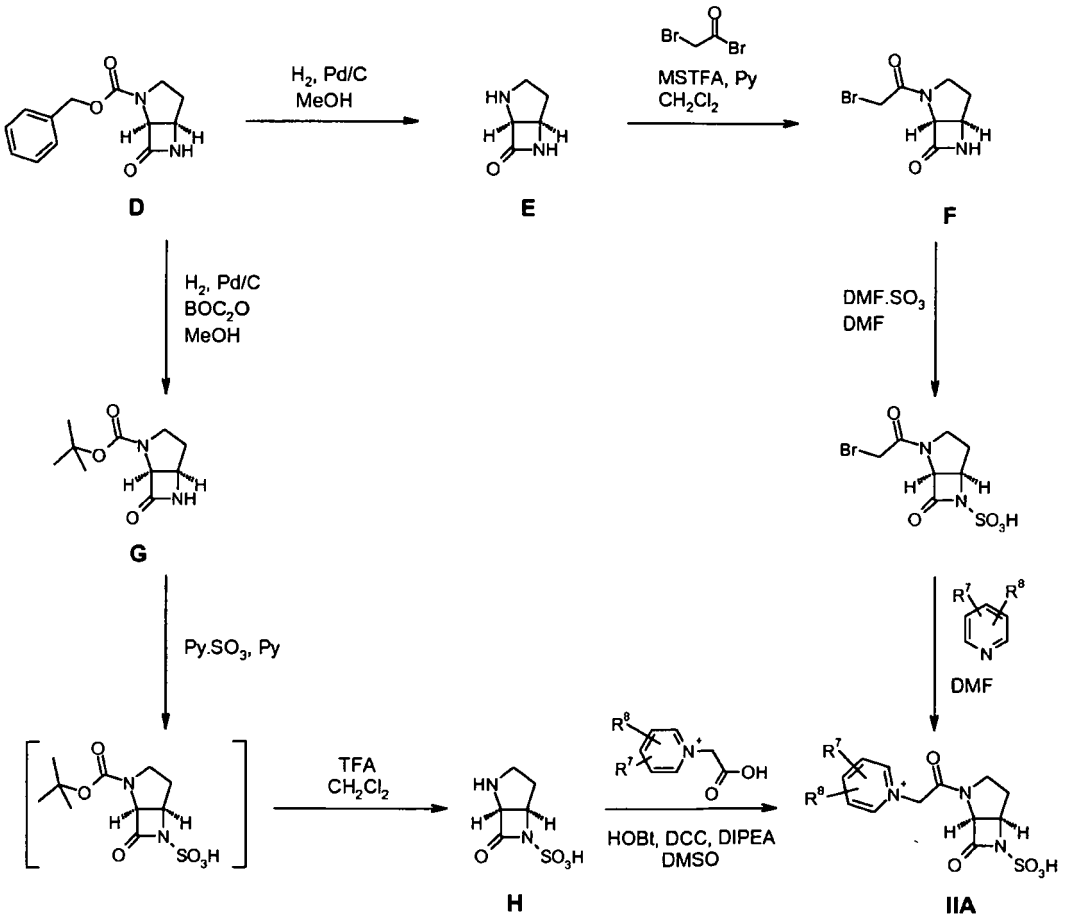


[0056] For the preparation of pyridinium carboxymethyl derivatives of formula IIA, two synthetic routes are possible (scheme 11) :

- First pathway: Compound F, prepared from compound D in presence of bromo acetyl bromide according to the procedures described in J. Med. Chem. 1998, 3961 and EP-A-0 508 234, may be sulfonated (J. Org. Chem. 1982, 5160). Pyridine derivatives, condensed at room temperature in dimethylformamide, are either commercially available or synthesized according to known literature procedures.
- Second pathway: Compound D may be first hydrogenated in presence of BOC_2O to afford the intermediate G (Tetrahedron Lett. 1988, 2983). Then sulfonation of compound G followed by removal of the BOC protecting group generates compound H (J. Med. Chem. 1998, 3961 and J. Org. Chem. 1982, 5160).

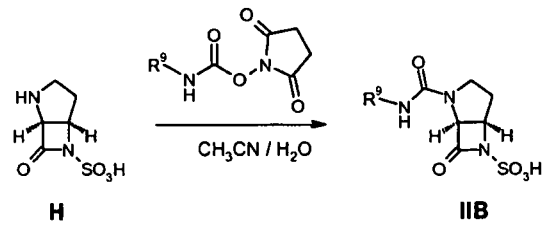
[0057] At that stage the pyridinium carboxymethyl derivatives (prepared by analogy according to the procedures described in Synthesis 2000, 1733 or J. Chem. Soc, Perkin Trans. I 1977, 1692) may be introduced to generate compounds IIA.

Scheme 11



[0058] The compounds of formula IIB may be obtained from compound H and succinimidyl derivatives according to the following scheme 12:

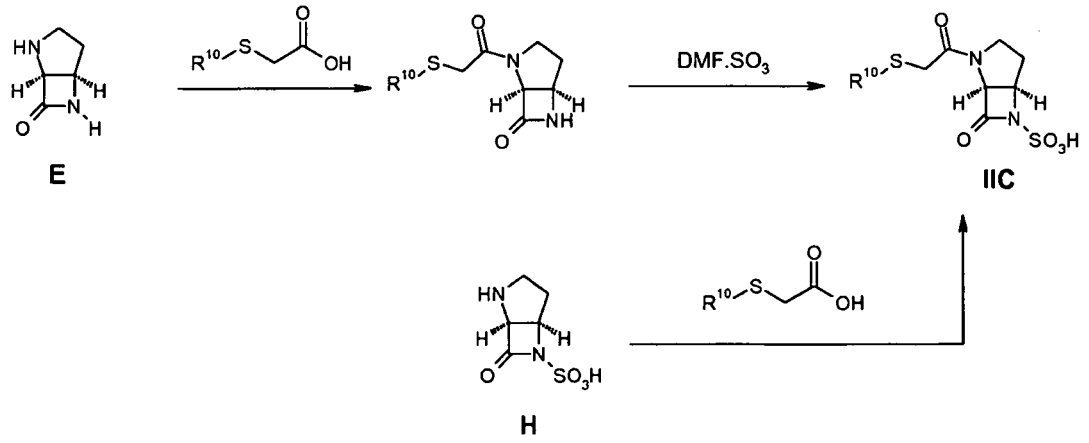
Scheme 12



[0059] Compound H may be prepared as previously described in scheme 11. Then the succinimidyl derivatives may be synthesized and introduced according to the procedures described in J. Med. Chem. 1998, 3961.

[0060] Compounds of formula IIC may be obtained either from compound E or compound H according to the following scheme 13:

Scheme 13



[0061] The compounds IIC may be synthesized via two different routes:

- either from compound E by first coupling with the thioacetic acid derivatives, followed by a sulfonation step (J. Med. Chem. 1998, 3961),
- or directly from compound H (see scheme 11) and thioacetic acid derivatives.

[0062] The preparation of sodium salt of compound of claim 1 and formula II can be performed either with the procedures described in WO-A-02/22613, US-B-6,566,355, J. Med. Chem. 1998, 3961 or in J. Antibiotics, 1985, 346.

[0063] In the above descriptions, the reactants are reacted together with a suitable solvent at elevated or low temperatures for sufficient time to allow the reaction to proceed to completion. The reaction conditions will depend upon the nature and reactivity of the reactants. Wherever a base is used in a reaction, they are selected from e.g. triethylamine, tributylamine, trioctylamine, pyridine, 4-dimethylaminopyridine, diisopropylamine, 1,5-diazabicyclo[4,3,0]non-5-ene, 1,8-diazabicyclo[5,4,0]undec-7-ene, sodium carbonate, sodium dicarbonate, potassium carbonate, potassium bicarbonate or cesium carbonate.

[0064] The deprotection of functional groups may be carried out either by hydrogenation or hydrolysis with appropriate acids such as hydrochloric acid, formic acid, trifluoroacetic acid, acetic acid or p-toluenesulfonic acid; in solvents such as methanol, ethanol, propanol, ethyl acetate, acetonitrile, methylene chloride or ethylene chloride. The hydrogenation is usually carried out in the presence of a metal catalyst, such as Pd, Pt or Rh under normal to high pressure.

[0065] The solvents of choice for the reaction are selected based upon the reactants used and from solvents such as benzene, toluene, acetonitrile, tetrahydrofurane, ethanol, methanol, chloroform, ethyl acetate, methylene chloride, dimethyl formamide, dimethyl sulfoxide, hexamethyl phosphoric triamide or the like. Solvents mixtures may also be used.

[0066] Reaction temperatures would generally range from between -70°C to 150°C. The preferred molar ratio of the reactants is 1:1 to 1:5. The reaction time range from 0.5 to 72 hours, depending on the reactants.

[0067] The compounds of claim 1 and their pharmaceutically compatible salts can be used in accordance with the invention in the control or prevention of illness in mammals, human and non-human, especially in combination with β-lactamase inhibitors.

[0068] Thereby, the compound of claim 1 or pharmaceutically compatible salts thereof with bases can be administered before, simultaneously with or after the administration or intake of one or more β-lactamase inhibitors of formula II-XIII. The products in accordance with the invention can be administered in the form of pharmaceutical compositions containing the combination of a compound of claim 1 or a pharmaceutically compatible salt thereof with a base, and one or more β-lactamase inhibitors of formula II-XIII; alternatively, they may also be administered separately from the β-lactamase inhibitors, simultaneously or sequentially, in which case the combination according to the invention may be present as a kit-of-parts. Articles with such pharmaceutical combinations are also suggested by of the present invention.

[0069] The compounds of claim 1 are active against a variety of bacterial organisms. They are active against aerobic Gram-negative bacteria that do not produce β-lactamase, including Enterobacteriaceae, for example *Escherichia coli, Enterobacter cloacae, Enterobacter aerogenes, Citrobacter freundii, Klebsiella pneumoniae, Klebsiella oxytoca, Proteus vulgaris, Providencia rettgeri; Pseudomonas* for example P. *aeruginosa; Acinetobacter* for example A. *baumannii; Burkholderia,* for example *B. cepacea; Stenotrophomonas* for example S. *maltophilia.* Combinations of compounds of claim 1 and β-lactamase inhibitors of formula II are active against strains of the above organisms that do produce β-lactamases and this activitiy can be increased by additionally combining β-lactamase inhibitors of formula III-XIII with the combination

comprising compounds of claim 1 and β-lactamase inhibitors of formula II.

FORMULATIONS

[0070] The pharmaceutical compositions and articles (kits-of-parts) suggested by the present invention are administered by any route, preferably in the form of a pharmaceutical composition, or kit-of-parts of individual compositions, adapted to such a route. Dosage and route of administration should be determined by susceptibility of the causative organisms, severity and site of infection, and the condition of the patient. The preferred types of pharmaceutical compositions are, for example, administered intravenously or by intramuscular injection.

[0071] Formulations for parenteral administration can be in the form of aqueous isotonic sterile injection solutions or suspensions. These solutions or suspensions can be prepared from sterile powders, granules or lyophilizates. The compounds can be dissolved in sterile water or in various sterile buffers that may contain sodium chloride, polyethylene glycol, propylene glycol, ethanol, sucrose, glucose, arginine, lysine, or lactic acid. The dry compositions can contain from 0.1% to 99% by weight, preferably 10% - 60% by weight, of each of active ingredients. If the compositions contain dosage units, each unit preferably contains from 50mg to 4g of each active substance.

[0072] The ratio of β-lactam antibiotic (compounds of claim 1 or pharmaceutically compatible salts thereof with a base) and β-lactamase inhibitors of formula II and formula III-XIII, or pharmaceutically compatible salts thereof with a base, can also vary within wide limits and will be fitted to the individual requirements in each particular case. In general, a ratio of between 1 part of antibiotic of claim 1 to 5 parts of any one β-lactamase inhibitor of general formula II or III-XIII and 20 parts of antibiotic of claim 1 to 1 part of any one β-lactamase inhibitor of general formula II or III-XIII should be appropriate.

[0073] The dosage of the compound of claim 1 and of the pharmaceutically compatible salts thereof with bases can vary within wide limits and will be fitted in each particular case to the individual requirements and to the β-lactamase producing pathogen to be controlled. In general, a dosage of about 0.1 to about 2 g of antibiotic administered one to four times over a 24 hours period should be appropriate.

[0074] The present invention is further illustrated by the following non-limiting examples.

Comparative Example 1

[0075] **(3*S*,4*S*)-3-{(2*Z*)-2-(2-amino(1,3-thiazol-4-yl))-3-[(5-hydroxy-1-methyl-4-oxo(2-hydropyridyl))methoxy]-3-azaprop-2-enoylamino}-4-methyl-2-oxoazetidinesulfonic acid** (6)

Preparation of 5-(diphenylmethoxy)-2-(hydroxymethyl)-1-methylhydropyridin-4-one

[0076] 5-(Diphenylmethoxy)-2-(hydroxymethyl)pyran-4-one (J. Antibiotics 1990, 189) (5.0 g, 16.22 mmol) and methyl amine (80,6 g, 1.04 mol) were stirred at room temperature overnight in presence of methanol (1 mL). The precipitate observed was filtered off and the mother liquor was extracted 3 times with ethyl acetate. The organic phases were dried and the solvent evaporated. The total amount of collected product was 2.1g.
1H-NMR (DMSO-d6) d: 3.49 (s, 3H), 4.29 (s, 2H), 6.22 (s, 1H), 6.74 (s, 1H), 7.20 - 7.60 (m, 11H) .

Preparation of 2-{[5-(diphenylmethoxy)-1-methyl-4-oxo-2-hydropyridyl] methoxy}benzo[c] azoline-1,3-dione

[0077] In THF (10.0 mL), containing triphenylphosphine (0.470 g, 1.79 mmol) and N-hydroxyphthalimide (0.293 g, 1.79 mmol) was added 5-(diphenylmethoxy)-2-(hydroxymethyl)-1-methylhydro-pyridin-4-one (0.240 g, 0.75 mmol). After cooling the solution at 0°C, diethyl-azodicarboxylate (0.312 g, 1.79 mmol) was added dropwise and stirred for 30 min at this temperature. The solution was then warmed up to room temperature and stirred overnight. A suspension was observed, filtered off and washed to give 210 mg of the desired compound.
1H-NMR (DMSO-d6) d: 3.78 (s, 3H), 5.08 (s, 2H), 6.29 (s, 1H), 6.74 (s, 1H), 7.20 - 7. 50 (m, 10H), 7.69 (s, 1H), 7.80 - 7.90 (m, 4H),

Preparation of 2-[(aminooxy)methyl]-5-(diphenylmethoxy)-1-methylhydro pyridin-4-one

[0078] Hydrazine hydrate (0.023 mL, 0.47 mmol) was added to ethanol (10 mL) already containing 2-{[5-(diphenylmethoxy)-1-methyl-4-oxo-2-hydropyridyl]methoxy}benzo[c] azoline-1,3-dione (0.200 g, 043 mmol). The resulting solution was refluxed for 2 hours. After cooling at room temperature the precipitate was collected and the ethanol was evaporated. The resulting residue was triturated in ethyl acetate to give 130 mg of the expected compound.
1H-NMR (DMSO-*d6*) d: 3.51 (s, 3H), 4.43 (s, 2H), 6.21 (s, 1H), 6.29 (br s, 2H), 6.74 (s, 1H), 7 .20 - 7.50 (m, 10H), 7.56 (s, 1H).

Preparation of (2*Z*)-3-{[5-(diphenylmethoxy)-1-methyl-4-oxo(2-hydropyridyl)] methoxy}-2-{2-[(triphenylmethyl)amino] (1,3-thiazol-4-yl)}-3-azaprop-2-enoic acid

[0079] In a mixture of ethanol (5 mL) / chloroform (3mL), 2-[(aminooxy)methyl]-5-(diphenylmethoxy)-1-methylhydropyridin-4-one (0.076 g, 0.23 mmol) and 2-oxo-2-{2-[(triphenylmethyl)amino](1,3-thiazol-4-yl)}acetic acid (0.085 g, 0.21 mmol) were stirred at room temperature for 12 hours. The solvents were evaporated and ethyl acetate was added to the residue. The resulting suspension was filtered off to afford 77 mg of the desired compound.
1H-NMR (DMSO-*d6*) d: 3.49 (s, 3H), 5.00 (s, 2H), 6.24 (s, 1H), 6.72 (s, 2H), 6.83 (s, 1H), 7.15 - 7.50 (m, 25H), 7.57 (s, 1H), 8.85 (s, 1H).

Preparation of (3*S*, 4*S*) -3- ((2*Z*)-3-{[5-(diphenylmethoxy)-1-methyl-4-oxo(2-hydropyridyl)]methoxy}-2-{2-[(triphenylmethyl)amino](1,3-thiazol-4-yl)}-3-azaprop-2-enoylamino)-4-methyl-2-oxoazetidinesulfonic acid

[0080] (2*Z*)-3-{[5-(diphenylmethoxy)-1-methyl-4-oxo(2-hydropyridyl)]methoxy}-2-{2-[(triphenyl methyl)amino](1,3-thiazol-4-yl)}-3-azaprop-2-enoic acid (0.380 g, 0.52 mmol), dicyclohexylcarbodiimide (0.160 g, 0.78 mmol) and 1-hydroxy-7-azabenzotriazole (0.106 g, 0.78 mmol) were stirred at room temperature for 3 hours. Then (3S,4S)-3-amino-4-methyl-2-oxoazetidinesulfonic acid (0.103 g, 1.04 mmol) and a catalytic amount of triethylamine were added to the previous solution which was stirred for 16 hours at room temperature. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (silica gel, eluent; dichloromethane and methanol, 95/5, v/v). 100 mg of desired compound was obtained.
1H-NMR (DMSO-d6) d: 1.35 (d, 3H, J = 6.0 Hz), 3.55 - 3.60 (m, 1H) 3.83 (s, 3H), 4.34 (dd, 1H, J = 2.5, 7.7 Hz), 5.21 (s, 2H), 6.75 (m, 1H), 6.77 (s, 1H), 7.00 (s br, 1H), 7.15 - 7.60 (m, 26H), 8.39 (s br, 1H) 8.83 (s, 1H), 9.33 (d, 1H, J = 7.7 Hz).

(3*S*,4*S*)-3-((2*Z*)-2-(2-amino(1,3-thiazol-4-yl))-3-[(5-hydroxy-1-methyl-4-oxo(2-hydropyridyl))methoxy]-3-azaprop-2-enoylamino}-4-methyl-2-oxoazetidinesulfonic acid (6)

[0081] (3*S*,4*S*)-3-((2*Z*)-3-{[5-(diphenylmethoxy)-1-methyl-4-oxo(2-hydropyridyl)]methoxy}-2-{2-[(triphenylmethyl) amino](1,3-thiazol-4-yl)}-3-azaprop-2-enoylamino)-4-methyl-2-oxoazetidinesulfonic acid (0.076 g, 0.08 mmol) was dissolved in dichloromethane (3 mL). Triethylsilane (0.021 mL, 0.25 mmol) was added at -10°C and trifluoroacetic acid (0.327 mL, 4.25 mmol) was added dropwise and stirred for 1h at the same temperature. The solution reacted at room temperature for 2 hours. Then dichloromethane was evaporated *in vacuo* and the residue was purified by preparative HPLC to give 35 mg of the desired compound.

Example 3

(3*S*,4*S*)-3-{(2*Z*)-2-(4-aminopyrimidin-2-yl)-3-[(1,5-dihydroxy-4-oxo(2-hydropyridyl))methoxy]-3-azaprop-2-enoylamino}-4-methyl-2-oxoazetidinesulfonic acid (21)

[0082] The titled compound was prepared following scheme 8. (2*Z*)-3-{[1,5-bis(diphenylmethoxy)-4-oxo(2-hydropyridyl)]methoxy}-2-{4-[(triphenylmethyl)amino]pyrimidin-2-yl}-3-azaprop-2-enoic acid was prepared according to the procedures described in J. Antibiotics, 1984, 546 and (3S,4S)-3-amino-4-methyl-2-oxoazetidinesulfonic acid was prepared according to the procedures described in J. Org. Chem. 1980, 410.
[0083] Final assembly and deprotection steps were done similarly according to the method described for the comparative example 1.
[0084] Compound 16 was prepared in analogy to the procedures described in WO-A-02/22613. The corresponding heterocycle of the carboxylic acid derivative of formula A was prepared in analogy to the procedures described in Z. Chem 1975, 233 and J. Antibiotics 1983, 1020.
[0085] Compound 20 was prepared in analogy to the procedures described in WO-A-02/22613. The corresponding heterocycle of the carboxylic acid derivative of formula A was prepared in analogy to the procedures described in US-A-4,394,504 but using 2-amino-6-picoline as starting material.
[0086] In the following table X the analytical data for all compounds of above formula (I) made are presented:

Table X

Compound Number (Example Number)	1H-NMR (DMSO-*d6*) δ in ppm	Mass m/z:
16	1.41 (d, 3H, *J* = 6.2 Hz), 3.62 (m, 1H), 4.44 (m, 1H), 5.27 (s, 2H), 6.76 (s, 1H), 7.83 (s, 1H), 8.10 (broad s, 2H), 9.64 (d, 1H, *J* = 7.7 Hz).	
20	1.43 (d, 3H, *J* = 6.2 Hz), 3.73 (m, 1H), 4.48 (m, 1H), 5.38 (s, 2H), 6.72 (d, 1H, *J* = 5.7 Hz), 6.83 (d, 1H, *J* = 5.7 Hz), 6.98 (s, 1H), 7.62 (t, 1H, *J* = 5.7 Hz), 8.04 (s, 1H), 9.54 (d, 1H, *J*= 7.7 Hz).	
21 (3)	1.43 (d, 3H), 3.67 (m, 1H),4.45 (m, 1H), 5.47 (s, 2H), 6.56 (s, 1H), 7.05 (s, 1H), 8.10 - 8.20 (m, 3H), 9.50 (d, 1H, *J* = 7.7 Hz)	

Comparative Example 14

(1*S*,5*R*)-2-[2-(3-carbamoyl-6-methylpyridinium)acetyl]-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate, inner salt (111)

[0087] The titled compound was prepared following scheme 11.

a) Preparation of 5-carbamoyl-1-carboxymethyl-2-methyl-pyridinium bromide

[0088] A solution of 6-methyl nicotinamide (400 mg, 2.94 mmol, 1.0 eq) and bromoacetic acid (408 mg, 2.94 mmol, 1.0 eq) in DMF (10 mL) was stirred at room temperature for 6 days. The reaction mixture was monitored by LCMS. Solvent was then evaporated and the crude product was purified by preparative HPLC to afford 136 mg of the expected compound.
1H-NMR (DMSO-d_6)δ (ppm): 2.80 (s, 3H); 5.66 (s, 2H); 8.13 (s, 1H); 8.24 (d, *J* = 8.3, 1H); 8.53 (s, 1H); 8.92 (dd, *J* = 1.8 and 8.3, 1H); 9.47 (s, 1H).

b) (1S,5R)-2-[2-(3-carbamoyl-6-methylpyridin-ium)acetyl]-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate, inner salt (111)

[0089] 5-carbamoyl-1-carboxymethyl-2-methyl-pyridinium bromide (91 mg, 0.47 mmol, 1.0 eq) was added at room temperature to a stirred solution of (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (J. Med. Chem. 1998, 3961) (90 mg, 0.47 mmol, 1.0 eq) in DMSO (4 mL), followed by 1-hydroxybenzotriazol (69 mg, 0.52 mmol, 1.1 eq), dicyclohexylcarbodiimide (106 mg, 0.52 mmol, 1.1 eq) and diisopropylethylamine (96 μL, 0.56 mmol, 1.2 eq). After stirring overnight at room temperature, the reaction mixture was filtered. The mother liquid was evaporated and the crude product was dissolved in CH_2Cl_2 (4 mL) and filtered. The resulting solid was purified by preparative HPLC to afford 46 mg of the expected compound.
1H-NMR (DMSO-d_6) δ (ppm): 1.82 (m, 1H); 2.42 (m, 1H); 2.73 (d, *J* = 5.3, 3H); 3.25 and 3.55 (2m, 1H); 4.05 (m, 1H); 4.40 and 4.62 (2t, *J* = 4.7, 1H); 5.19 and 5.31 (2d, *J* = 4.3, 1H); 5.55-6.05 (AB part of a ABX system, the X part being in the ^{15}N spectrum, 2H); 8.12 (d, *J* = 7.0, 1H); 8.22 (d, *J* = 8.3, 1H); 8.53 (d, *J* = 10.0, 1H); 8.89 (dd, *J* = 1.8 and 8.3, 1H); 9.36 (dd, *J* = 1.8 and 10.0, 1H).

Comparative Example 15

(1*S*,5*R*)-2-{2-[3-(N-methylcarbamoyl)pyridinium]acetyl}-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate,inner salt (101)

[0090] The titled compound was prepared following scheme 11 and in analogy to example 14 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available N-methyl nicotinamide as starting materials.
+ESI-MS spectrum: m/z: 289 $[M+H-SO_3]^+$.

Comparative Example 16

(1*S*,5*R*)-2-[2-(4-aminopyridinium)acetyl]-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate, inner salt (103)

[0091] The titled compound was prepared following scheme 11 and in analogy to example 14 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 4-aminopyridine as starting materials.
+ESI-MS spectrum: m/z: 326 $[M]^+$.

Comparative Example 17

(1*S*,5*R*)-2-(2-(2-isoquinolinium)acetyl)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate, inner salt (104)

[0092] The titled compound was prepared following scheme 11 and in analogy to example 14 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available isoquinoline as starting materials.
-ESI-MS spectrum: m/z: 360 $[M-1]^+$.

Comparative Example 18

(1*S*,5*R*)-2-[2-(4-carbamoylpyridinium)acetyl]-7-oxo-2,6-diazabicyclo[3.2.0] heptane-6-sulfonate, inner salt (105)

[0093] The titled compound was prepared following scheme 11 and in analogy to example 14 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available isonicotinamide as starting materials.
1H-NMR (DMSO-d_6): 1.78 (m, 1H); 2.40 (m, 1H); 3.20 and 3.50 (2m, 1H); 4.05 and 4.12 (2m, 1H); 4.43 and 4.60 (2t, *J* = 4.7, 1H); 5.21 and 5.29 (2d, *J* = 4.3, 1H); 5.55-6.00 (AB part of a ABX system, the X part being in the ^{15}N spectrum, 2H); 8.27 (m, 1H); 8.46 (m, 2H); 8.65 (m, 1H); 9.12 (m, 2H).

Comparative Example 19

(1*S*,5*R*)-7-oxo-2-(2-(2-5,6,7,8-tetrahydroisoquinolinium)acetyl)-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate, inner salt (106)

[0094] The titled compound was prepared following scheme 11 and in analogy to example 14 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 5,6,7,8-tetrahydroisoquinoline as starting materials.
+ESI-MS spectrum: m/z: 365 $[M]^+$.

Comparative Example 20

(1*S*,5*R*)-2-[2-(3-aminopyridinium)acetyl]-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate, inner salt (107)

[0095] The titled compound was prepared following scheme 11 and in analogy to example 14 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 3-aminopyridine as starting materials.
+ESI-MS spectrum: m/z: 326 $[M]^+$.

Comparative Example 21

(1*S*,5*R*)-2-(2-{3-[N-(carbamoylmethyl)carbamoyl]pyridinium}acetyl)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate, inner salt (108)

[0096] The titled compound was prepared following scheme 11 and in analogy to example 14 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and 3-[N-(carbamoylmethyl)carbamoyl]pyridine as starting materials.
+ESI-MS spectrum: m/z: 411 $[M]^+$.
[0097] 3-[*N*-(carbamoylmethyl)carbamoyl]pyridine was prepared by reacting the commercially available nicotinyl chlo-

ride hydrochloride with glycinamide hydrochloride.

Comparative Example 22

(1*S*, 5*R*) -2-{2- [3- (N-cyclopropylcarbamoyl)pyridinium]acetyl}-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate, inner salt (109)

[0098] The titled compound was prepared following scheme 11 and in analogy to example 14 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available nicotinoyl chloride hydrochloride and cyclopropylamine as starting materials.
1H-NMR (DMSO-d_6) : 0.60 (m, 2H); 0.78 (m, 2H); 1.77 (m, 1H); 2.40 (m, 1H); 2.92 (m, 1H); 3.23 and 3.50 (2m, 1H); 4.01 and 4.10 (2m, 1H); 4.41 and 4.61 (2t, *J*= 4.7, 1H); 5.20 and 5.29 (2d, *J* = 4.3, 1H); 5.58-6.05 (AB part of a ABX system, the X part being in the ^{15}N spectrum, 2H); 8.30 (m, 1H); 8.95 (m, 1H); 9.01-9.13 (m, 2H); 9.36 (m, 1H).

Comparative Example 23

(1*S*,5*R*)-2-{2-[4-(dimethylamino)pyridinium]acetyl}-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate, inner salt (112)

[0099] The titled compound was prepared following scheme 11 and in analogy to example 14 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 4-(dimethylamino)pyridine as starting materials.
1H-NMR (DMSO-d_6) : 1.22 (s, 3H); 1.26 (s, 3H); 1.74 (m, 1H); 2.38 (m, 1H); 3.20-3.50 (m, 1H); 3.98 and 4.08 (2dd, *J* = 8.6 and 11.2, 1H); 4.38 and 4.48 (2t, *J* = 4.7, 1H); 5.00-5.45 (m, 3H); 7.02 and 7.07 (2d, *J*= 7.9, 2H); 8.11 and 8.16 (2d, *J* = 7.9, 2H).

Comparative Example 24

2-(2-{3-[N-((3S)pyrrolidin-3-yl)carbamoyl]pyridinium}acetyl)(1S,5R)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate, inner salt (122)

Preparation of sodium (1S,5R)-2-(2-bromoacetyl)-7-oxo-2,6-diazabicyclo[3.2.0] heptane-6-sulfonate

[0100] A solution of sulphur trioxide.DMF complex (4.92 g, 32.10 mmol, 1.5 eq) in DMF (10 mL) was added at 0 °C to a stirred solution of (5*S*,1*R*)-4-(2-bromoacetyl)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound F, 5.25 g, 21.40 mmol, 1.0 eq) in DMF (110 mL). After 5 hours stirring at 0 °C, the reaction mixture was concentrated. The remaining oil was dissolved in a minimum amount of H_2O and the pH was adjusted to 6 with saturated $NaHCO_3$ solution. The mixture was then concentrated under reduced pressure to afford 8.3 g of the expected sodium (1*S*,5*R*)-2-(2-bromoacetyl)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate as a brown oil.

Preparation of *tert*-butyl (3*S*)-3-(3-pyridylcarbonyl-amino)pyrrolidinecarboxylate

[0101] Nicotinoyl chloride hydrochloride (286 mg, 1.61 mmol, 1.0 eq) was added at room temperature to a stirred solution of (S)-3-amino-1-N-BOC-pyrrolidine (300 mg, 1.61 mmol, 1.0 eq) in CH_2Cl_2 (9 mL), followed by triethylamine (337 μL, 2.42 mmol, 1.5 eq). After stirring overnight at room temperature, the reaction mixture was extracted and the organic layer was dried over Na_2SO_4, filtered and evaporated to afford 457 mg of the expected compound.

Preparation of 2-{2-[3-(N-{(3*S*)-1-[(tert-butyl)oxycarbonyl]pyrrolidin-3-yl}carbamoyl)pyridinium]acetyl}(1*S*,5*R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate, inner salt

[0102] A solution of (1*S*,5*R*)-2-(2-bromoacetyl)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (200 mg, 0.64 mmol, 1.0 eq) and *tert*-butyl (3*S*)-3-(3-pyridylcarbonyl-amino)pyrrolidinecarboxylate (149 mg, 0.51 mmol, 0.8 eq) in DMF (2 mL) was stirred at room temperature for 3 days. The reaction was monitored by LCMS. Then DMF was evaporated to afford 330 mg the expected crude product which was directly used in the next step.

Preparation of 2-(2-{3-[N-((3S)pyrrolidin-3-yl)carbamoyl]pyridinium}acetyl)-(1*S*,5*R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate, inner salt (122)

[0103] A solution of 2-{2-[3-(N-{(3*S*)-1-[(tert-butyl)oxycarbonyl]pyrrolidin-3-yl)carbamoyl)pyridinium] acetyl}(1*S*, 5*R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate, inner salt in DMF (4 mL) was cooled to 0 °C before the addition of trifluoroacetic acid (729 μL, 9.45 mmol, 15.0 eq). After stirring overnight at room temperature, the reaction mixture was concentrated and the crude was purified by preparative HPLC to afford 37 mg of the expected compound.
1H-NMR (DMSO-d_6): 1.80 (m, 1H); 2.05 (m, 1H); 2.23 (m, 1H); 2.40 (m, 1H); 3.33 (m, 5H); 4.01 and 4.10 (2m, 1H); 4.13 and 4.61 (2t, *J* = 4.7, 1H); 4.56 (m, 1H); 5.18 and 5.30 (2d, *J* = 4.1, 1H); 5.60-6.05 (AB part of an ABX system, the X part being in the ^{15}N spectrum, 2H); 8.35 (m, 1H); 9.07 (m, 3H); 9.38 (m, 1H); 9.44 (s, 1H) .

Comparative Example 25

(1*S*,5*R*)-2-[2-(3-carbamoylpyridinium)acetyl]-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate, inner salt (102)

[0104] The titled compound was prepared following scheme 11 and in analogy to example 24 using (5*S*,1*R*)-4-(2-bromoacetyl)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound F) which was first sulfonated (J. Org. Chem. 1982, 5160) and the commercially available nicotinamide as starting materials.

[0105] 1H-NMR (DMSO-d_6) : 1.78 (m, 1H); 2.40 (m, 1H); 3.23 and 3.50 (2m, 1H); 4.03 and 4.13 (2dd, *J* = 8.6 and 11.0, 1H); 4.42 and 4.63 (2t, *J* = 4.7, 1H); 5.20 and 5.32 (2d, *J* = 4.3, 1H); 5.55-6.05 (AB part of a ABX system, the X part being in the ^{15}N spectrum, 2H); 8.18 (d, *J* = 3.7, 1H); 8.33 (q, *J* = 6.2 and 7.9, 1H); 8.57 and 8.62 (2s, 1H); 9.02-9.12 (m, 2H); 9.42 (d, *J* = 6.5, 1H).

Comparative Example 26

(1*S*,5*R*)-2-[2-(3,4-dicarbamoylpyridinium)acetyl]-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate, inner salt (110)

[0106] The titled compound was prepared following scheme 11 and in analogy to example 24 using (5*S*,1*R*)-4-(2-bromoacetyl)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound F) which was first sulfonated (J. Org. Chem. 1982, 5160) and the commercially available 3,4-pyridine dicarboxamide as starting materials.
1H-NMR (DMSO-d_6): 1.74 (m, 1H); 2.40 (m, 1H); 3.25 and 3.49 (2m, 1H); 4.03 and 4.11 (2m, 1H); 4.41 and 4.62 (2t, *J* = 4.7, 1H); 5.22 and 5.29 (2d, *J* = 4.3, 1H); 5.55-6.00 (AB part of a ABX system, the X part being in the ^{15}N spectrum, 2H); 8.04 (m, 1H) ; 8.14 (d, *J* = 10.8, 1H); 8.24 (m, 2H); 8.45 (d, *J* = 9.1, 1H) ; 9.10 (m, 1H) ; 9.24 (2s, 1H) .

Comparative Example 27

(1*S*,5*R*)-2-{2-[4-(isopropyl)pyridinium]acetyl}-7-oxo-2,6-diazabicyclo[3.2.0] heptane-6-sulfonate, inner salt (113)

[0107] The titled compound was prepared following scheme 11 and in analogy to example 24 using (5*S*,1*R*)-4-(2-bromoacetyl)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound F) which was first sulfonated (J. Org. Chem. 1982, 5160) and the commercially available 4-isopropyl pyridine as starting materials.
1H-NMR (DMSO-d_6) : 1.28 and 1.30 (2d, *J* = 2.3, 6H); 1.77 (m, 1H); 2.42 (m, 1H); 3.10-3.55 (m, 2H); 4.00 and 4.10 (2m, 1H); 4.40 and 4.60 (2t, *J* = 4.7, 1H); 5.19 and 5.29 (2d, *J* = 4.2, 1H); 5.45-5.90 (AB part of a ABX system, the X part being in the ^{15}N spectrum, 2H); 8.11 (m, 2H); 8.81 (d, *J* = 6.7, 1H); 8.87 (d, *J* = 7.1, 1H).

Comparative Example 28

(1*S*,5*R*)-2-{2-[3-(methoxycarbonyl)-5-methylpyridin-ium]acetyl}-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate, inner salt (114)

[0108] The titled compound was prepared following scheme 11 and in analogy to example 24 using (5*S*,1*R*)-4-(2-bromoacetyl)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound F) which was first sulfonated (J. Org. Chem. 1982, 5160) and the commercially available methyl-5-methylnicotinate as starting materials.
1H-NMR (DMSO-d_6): 1.77 (m, 1H); 2.41 (m, 1H); 2.58 (d, *J* = 5.9, 3H); 3.24 and 3.49 (2m, 1H); 3.98 (d, *J* = 2.5, 3H); 4.02 and 4.12 (2m, 1H); 4.41 and 4.61 (2t, *J* = 4.7, 1H); 5.20 and 5.29 (2d, *J* = 4.3, 1H); 5.55-6.00 (AB part of a ABX system, the X part being in the ^{15}N spectrum, 2H); 8.95 (m, 1H); 9.06 and 9.15 (2s, 1H); 9.41 and 9.45 (2s, 1H).

Comparative Example 29

(1*S*,5*R*)-2-{2-[3-(methoxycarbonyl)-2-methylpyridin-ium]acetyl}-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate, inner salt (115)

[0109] The titled compound was prepared following scheme 11 and in analogy to example 24 using (5*S*,1*R*)-4-(2-bromoacetyl)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound F) which was first sulfonated (J. Org. Chem. 1982, 5160) and the commercially available 2-methyl nicotinic acid methyl ester as starting materials.
1H-NMR (DMSO-d_6): 1.82 (m, 1H); 2.40 (m, 1H); 2.81 (d, *J* = 2.8, 3H); 3.29 and 3.57 (2m, 1H); 3.96 (s, 3H); 4.06 (m, 1H); 4.40 and 4.62 (2t, *J* = 4.8, 1H); 5.20 and 5.34 (2d, *J* = 4.3, 1H); 5.65-6.05 (AB part of a ABX system, the X part being in the ^{15}N spectrum, 2H); 8.17 (m, 1H); 8.91 (m, 1H); 9.08 (m, 1H).

Comparative Example 30

(1*S*,5*R*)-2-{2-[3-(methoxycarbonyl)pyridinium]acetyl}-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate, inner salt (116)

[0110] The titled compound was prepared following scheme 11 and in analogy to example 24 using (5*S*,1*R*)-4-(2-bromoacetyl)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound F) which was first sulfonated (J. Org. Chem. 1982, 5160) and the commercially available 3-carboxypyridine methyl ester as starting materials.
1H-NMR (DMSO-d_6) : 1.80 (m, 1H) ; 2.39 (m, 1H); 3.22 and 3.52 (2m, 1H); 3.98 (d, *J* = 2.3, 3H); 4.01 and 4.12 (2m, 1H); 4.41 and 4.61 (2t, *J* = 4.7, 1H); 5.20 and 5.29 (2d, *J* = 4.2, 1H); 5.65-6.05 (AB part of a ABX system, the X part being in the ^{15}N spectrum, 2H); 8.35 (m, 1H); 9.07 (m, 1H); 9.13 and 9.21 (2m, 1H); 9.57 and 9.62 (2s, 1H); 12.75 (br, 1H).

Comparative Example 31

(1*S*,5*R*)-7-oxo-2-[2-(4-propanoylpyridinium)acetyl]-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate, inner salt (117)

[0111] The titled compound was prepared following scheme 11 and in analogy to example 24 using (5*S*,1*R*)-4-(2-bromoacetyl)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound F) which was first sulfonated (J. Org. Chem. 1982, 5160) and the commercially available 4-propionyl pyridine as starting materials.
1H-NMR (DMSO-d_6): 1.13 (dt, *J* = 2.5 and 7.1, 3H); 1.80 (m, 1H); 2.41 (m, 1H); 3.15-3.55 (m, 3H); 4.02 and 4 . 11 (2dd, *J* = 8.8 and 11.1, 1H); 4.41 and 4.61 (2t, *J* = 4.7, 1H); 5.20 and 5.29 (2d, *J* = 4.3, 1H); 5.60-6.05 (AB part of a ABX system, the X part being in the ^{15}N spectrum, 2H); 8.53 and 8.56 (2d, *J* = 7.1, 2H); 9.11 and 9.18 (2d, *J*= 7.1, 2H).

Comparative Example 32

(1*S*,5*R*)-2-{2-[4-(aminothioxomethyl)pyridinium]acetyl}-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate, inner salt (118)

[0112] The titled compound was prepared following scheme 11 and in analogy to example 24 using (5*S*,1*R*)-4-(2-bromoacetyl)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound F) which was first sulfonated (J. Org. Chem. 1982, 5160) and the commercially available 4-pyridine carbothioamide as starting materials.
1H-NMR (DMSO-d_6) : 1.79 (m, 1H); 2.39 (m, 1H); 3.24 and 3.49 (2m, 1H); 4.00 and 4.10 (2m, 1H); 4.41 and 4.61 (2t, *J* = 4.7, 1H); 5.21 and 5.28 (2d, *J* = 4.3, 1H); 5.55-5.95 (AB part of a ABX system, the X part being in the ^{15}N spectrum, 2H); 8.28 (dd, *J* = 6.8 and 10.8, 2H); 8.96 and 9.02 (2d, *J* = 6.8, 2H); 10.31 and 10.74 (2br, 2H); 12.7 (br, 1H).

Comparative Example 33

(1S,5R)-2-(2-{3-[(ethoxycarbonyl)methyl]pyridinium}acetyl)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate, inner salt (119)

[0113] The titled compound was prepared following scheme 11 and in analogy to example 24 using (5S,1R)-4-(2-bromoacetyl)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound F) which was first sulfonated (J. Org. Chem. 1982, 5160) and the commercially available ethyl-3-pyridyl acetate as starting materials.
1H-NMR (DMSO-d_6) : 1.22 (dt, *J* = 0.9 and 7.1, 3H); 1.75 (m, 1H); 2.41 (m, 1H); 3.22 and 3.49 (2m, 1H); 4.05 (m, 3H); 4.15 (dq, *J* = 0.9 and 7.1, 2H); 4.40 and 4.61 (2t, *J* = 4.6, 1H); 5.20 and 5.30 (2d, *J* = 4.3, 1H); 5.50-5.95 (AB part of a ABX system, the X part being in the ^{15}N spectrum, 2H); 8.19 (m, 1H); 8.61 (m, 1H); 8.87 and 8.92 (2m, 1H); 8.89 and

8.97 (2s, 1H).

Comparative Example 34

(1S,5R)-7-oxo-2-{2-[3-(trifluoro-methyl)pyridinium]acetyl}-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate, inner salt (120)

[0114] The titled compound was prepared following scheme 11 and in analogy to example 24 using (5*S*,1*R*)-4-(2-bromoacetyl)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound F) which was first sulfonated (J. Org. Chem. 1982, 5160) and the commercially available 3-(trifluoromethyl)pyridine as starting materials.
1H-NMR (DMSO-d_6): 1.80 (m, 1H); 2.40 (m, 1H); 3.24 and 3.51 (2m, 1H); 4.04 and 4.12 (2m, 1H); 4.42 and 4.62 (2t, *J* = 4.7, 1H); 5.21 and 5.29 (2d, *J* = 4.1, 1H); 5.65 - 6.05 (AB part of a ABX system, the X part being in the ^{15}N spectrum, 2H); 8.47 (m, 1H); 9.17 (m, 1H); 9.24 and 9.30 (2d, *J* = 6.2, 1H); 9.67 and 9.76 (2s, 1H); 12.7 (br, 1H).

Comparative Example 35

(1*S*,5*R*)-2-[2-(3,4-dimethylpyridinium)acetyl]-7-oxo-2,6-diazabicyclo[3.2.0] heptane-6-sulfonate, inner salt (121)

[0115] The titled compound was prepared following scheme 11 and in analogy to example 24 using (5*S*,1*R*)-4-(2-bromoacetyl)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound F) which was first sulfonated (J. Org. Chem. 1982, 5160) and the commercially available 3,4-lutidine as starting materials.
1H-NMR (DMSO-d_6) : 1.78 (m, 1H) ; 2.40 (d, *J* = 3.7, 3H); 2.47 (m, 1H); 2.55 (d, *J* = 3.6, 3H); 3.21 and 3.49 (2m, 1H); 4.06 (m, 1H); 4.40 and 4.60 (2t, *J* = 4.7, 1H); 5.20 and 5.28 (2d, *J* = 4.3, 1H); 5.40-5.85 (AB part of a ABX system, the X part being in the ^{15}N spectrum, 2H); 7.97 (m, 1H); 8.70 (m, 2H).

Comparative Example 36

(1*S*,5*R*)-7-oxo-2-{2-[3-benzylpyridinium]acetyl}-2,6-di-azabicyclo[3.2.0]heptane-6-sulfonate, inner salt (123)

[0116] The titled compound was prepared following scheme 11 and in analogy to example 24 using (5*S*,1*R*)-4-(2-bromoacetyl)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound F) which was first sulfonated (J. Org. Chem. 1982, 5160) and the commercially available 3-benzylpyridine as starting materials.
1H-NMR (DMSO-d_6) : 1.78 (m, 1H) ; 2.40 (m, 1H) ; 3.21 and 3.41 (2m, 1H); 4.01 and 4.10 (2m, 1H); 4.21 (d, *J* = 7.3, 2H); 4.40 and 4.60 (2t, *J* = 4.7, 1H); 5.20 and 5.28 (2d, *J* = 4.2, 1H); 5.50-5.95 (AB part of a ABX system, the X part being in the ^{15}N spectrum, 2H); 7.31 (m, 5H); 8.12 (m, 1H); 8.55 (t, *J* = 7.6, 1H); 8.80 and 8.85 (2d, *J* = 6.3, 1H); 8.90 and 9.00 (2s, 1H).

Comparative Example 37

(1*S*,5*R*)-7-oxo-2-[2-(3-phenylpyridinium)acetyl]-2,6-di-azabicyclo[3.2.0]heptane-6-sulfonate, inner salt (124)

[0117] The titled compound was prepared following scheme 11 and in analogy to example 24 using (5*S*,1*R*)-4-(2-bromoacetyl)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound F) which was first sulfonated (J. Org. Chem. 1982, 5160) and the commercially available 3-phenyl pyridine as starting materials.
1H-NMR (DMSO-d_6): 1.80 (m, 1H); 2.40 (m, 1H); 3.23 and 3.51 (2m, 1H); 4.10 (m, 1H); 4.42 and 4.62 (2t, *J* = 4.7, 1H); 5.21 and 5.33 (2d, *J* = 4.2, 1H); 5.60-6.00 (AB part of a ABX system, the X part being in the ^{15}N spectrum, 2H); 7.62 (m, 3H); 7.88 (m, 2H); 8.28 (m, 1H); 8.93 (2d, *J* = 6.3, 1H); 8.99 (m, 1H); 9.41 and 9.48 (2s, 1H).

Comparative Example 38

2-(2-{3-[N-((3*R*)pyrrolidin-3-yl)carbamoyl]pyridinium}acetyl)(1S,5R)-7-oxo-2,6-diazabicy-clo[3.2.0]heptane-6-sulfonate, inner salt (125)

[0118] The titled compound was prepared following scheme 11 and in analogy to example 24 using (5*S*,1*R*)-4-(2-bromoacetyl)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound F) which was first sulfonated (J. Org. Chem. 1982, 5160) and the commercially available nicotinoyl chloride hydrochloride and (*R*)-3-amino-1-N-BOC-pyrrolidine as starting materials.
+ESI-MS spectrum: m/z: 423 $[M]^+$.

Comparative Example 39

(1*S*,5*R*)-2-[2-(4-amino-3-carbamoylpyridinium)acetyl]-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate, inner salt (126)

[0119] The titled compound was prepared following scheme 11 and in analogy to example 24 using (5*S*,1*R*)-4-(2-bromoacetyl)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound F) which was first sulfonated (J. Org. Chem. 1982, 5160) and a the commercially available 4-amino-3-pyridinecarboxamide as starting materials.
1H-NMR (DMSO-d_6) : 1.75 (m, 1H) ; 2.40 (m, 1H) ; 3.22 and 3.45 (2m, 1H); 4.01 and 4.10 (2dd, *J* = 8.6 and 11.3, 1H); 4.40 and 4.60 (2t, *J* = 4.8, 1H); 4.95-5.50 (m, 3H); 7.03 (dd, *J* = 7.4 and 9.4, 1H); 7.83 (br, 1H); 8.05 (m, 1H); 8.15 (br, 1H); 8.65 (m, 1H); 8.99 and 9.04 (2br, 2H).

Comparative Example 40

(1*S*,5*R*)-2-[2-(3-carbamoyl-5-methylpyridinium)acetyl]-7-oxo-2,6-diazabicyclo[3.2.0] heptane-6-sulfonate, inner salt (127) .

[0120] The titled compound has been prepared following scheme 11 and in analogy to example 24 using (5*S*,1*R*)-4-(2-bromoacetyl)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound F) which was first sulfonated (J. Org. Chem. 1982, 5160) and the commercially available 5-methyl nicotinamide as starting materials.
1H-NMR (DMSO-d_6): 1.78 (m, 1H); 2.39 (m, 1H); 2.54 (m, 3H); 3.23 and 3.49 (2m, 1H); 4.05 (m, 1H); 4.41 and 4.61 (2t, *J* = 4.7, 1H); 5.20 and 5.29 (2d, *J* = 4.3, 1H); 5.50-6.00 (AB part of a ABX system, the X part being in the ^{15}N spectrum, 2H); 8.52 (d, *J* = 16.0, 1H); 8.89 (d, *J* = 7.2, 1H); 8.95 and 9.04 (2s, 1H); 9.24 (m, 2H); 12.6 (br, 1H).

Comparative Example 41

(1*S*,5*R*)-2-{2-[3-(aminocarbonylamino)pyridinium]acetyl}-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate, inner salt (128) .

[0121] The titled compound has been prepared following scheme 11 and in analogy to example 24 using (5*S*,1*R*)-4-(2-bromoacetyl)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound F) which was first sulfonated (J. Org. Chem. 1982, 5160) and 3-pyridylcarbamide.
1H-NMR (DMSO-d_6): 1.78 (m, 1H); 2.40 (m, 1H); 3.23 and 3.49 (2m, 1H); 3.98 and 4.10 (2m, 1H); 4.40 and 4.59 (2t, *J* = 4.7, 1H); 5.20 and 5.28 (2d, *J* = 4.2, 1H); 5.40-6.00 (AB part of a ABX system, the X part being in the ^{15}N spectrum, 2H); 6.51 (br, 2H); 8.00 (m, 1H); 8.28 (m, 1H); 8.49 (m, 1H); 9.20 (m, 1H) ; 9.67 (d, *J* = 12.2, 1H) .
[0122] 3-Pyridylcarbamide was prepared according to the procedure described in Heterocycles 1983, 1899.

Comparative Example 42

(1*S*,5*R*)-2-[2-(5-amino-3-carbamoylpyridinium)acetyl]-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate, inner salt (129).

[0123] The titled compound has been prepared following scheme 11 and in analogy to example 24 using (5*S*,1*R*)-4-(2-bromoacetyl)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound F) which was first sulfonated (J. Org. Chem. 1982, 5160) and the commercially available 5-amino-3-pyridinecarboxamide as starting materials.
1H-NMR (DMSO-d_6): 1.78 (m, 1H); 2.41 (m, 1H); 3.22 and 3.46 (2m, 1H); 3.98 and 4.09 (2m, 1H); 4.40 and 4.59 (2t, *J* = 4.6, 1H); 5.20 and 5.26 (2d, *J* = 4.1, 1H); 5.40-5.85 (AB part of a ABX system, the X part being in the ^{15}N spectrum, 2H); 6.88 (d, *J* = 11.5, 2H); 7.95 (m, 1H); 8.07 (m, 2H); 8.41 (m, 2H).

Comparative Example 43

(1*S*,5*R*)-2-[N-(4-{[(2-amino-ethyl)amino]carbonylamino}phenyl)carbamoyl]-7-oxo-2,6-di-azabicyclo[3.2.0]heptane-6-sulfonic acid (324)

Preparation of (*tert*-butoxy)-N-{4-[(fluoren-9-ylmeth-oxy)carbonylamino]phenyl} carboxamide

[0124] Triethylamine (7.36 mL, 52.82 mmol, 1.1 eq) was added at 0 °C to a stirred solution of *N*-BOC-1,4-phenylene diamine (10.00 g, 48.02 mmol, 1.0 eq) in CH_3CN (240 mL), followed by 9-fluorenylmethyloxycarbonyl chloride (14.90

g, 57.62 mmol, 1.2 eq). The resulting mixture was allowed to come at room temperature. After 4 hours stirring at room temperature, the reaction mixture was filtered to afford 20.60 g of the crude expected product as a white powder which was used in the next step without any further purification.
1H-NMR (DMSO-d_6) : 1. 46 (s, 9H); 4.29 (t, *J*= 6.6, 1H) ; 4.44 (d, *J*= 6.3, 2H); 7.30-7.45 (m, 8H); 7.75 (d, *J*= 7.4, 2H); 7.91 (d, *J*= 7.4, 2H); 9.22 (br, 1H); 9.59 (br, 1H).

Preparation of N-(4-aminophenyl)(fluoren-9-ylmeth-oxy)carboxamide

[0125] TFA (55.30 mL, 717.76 mmol, 15.0 eq) was added at 0 °C to a stirred solution of (*tert*-butoxy)-N-{4-[(fluoren-9-yl-methoxy)carbonylamino]phenyl}carboxamide_(20.60 g, 47.85 mmol, 1.0 eq) in CH_2Cl_2 (900 mL). The resulting solution was allowed to come at room temperature. After stirring overnight at room temperature, the reaction mixture was concentrated to dryness and the residue was triturated in water. Then the mixture was filtered to afford 15.80 g of the expected crude product as a white powder.
1H-NMR (DMSO-d_6) : 4.30 (t, *J* = 6.4, 1H) ; 4.49 (d, *J* = 6.4, 2H); 7.06 (d, *J* = 7.7, 2H); 7.40 (m, 6H); 7.74 (d, *J*= 7.4, 2H); 7.91 (d, *J* = 7.4, 2H); 8.95 (br, 2H); 9.73 (br, 1H) .

Preparation of N-{4-[(2,5-dioxoazolidiny-loxy)carbonylamino]phenyl}(fluoren-9-ylmethoxy)carboxamide

[0126] *N,N*'-Disuccinimidylcarbonate (16.20 g, 63.26 mmol, 1.1 eq) was added at room temperature to a stirred solution of N-(4-aminophenyl)(fluoren-9-ylmethoxy)carboxamide (20.00 g, 60.53 mmol, 1.0 eq) in CH_3CN (1100 mL). After stirring overnight at room temperature, the reaction mixture was filtered to afford 28.50 g of the expected crude product as a white powder.
1H-NMR (DMSO-d_6): 2.83 (br, 4H); 4.31 (t, *J*= 6.4, 1H); 4.48 (m, 2H); 7.20-7.50 (m, 8H); 7.5 (d, *J* = 7.4, 2H); 7.91 (d, *J* = 7.4, 2H); 9.72 (br, 1H); 10.67 (br, 1H).

Preparation of N-{4-[({2-[(*tert*-butoxy)carbonylamino]ethyl}amino)carbonylamino]phenyl}(fluoren-9-ylmethoxy)carboxamide

[0127] A solution of N-{4-[(2,5-dioxoazolidiny-loxy)carbonylamino]phenyl}(fluoren-9-ylmethoxy)carboxamide (16.10 g, 34.15 mmol, 1.0 eq) in H_2O/CH_3CN (1/1, v/v, 360 mL) was reacted at room temperature with $NaHCO_3$ (2.86 g, 34.15 mmol, 1.0 eq) and N-BOC-ethylene diamine (5.47 g, 34.15 mmol, 1.0 eq). After stirring overnight at room temperature, the reaction mixture was filtered to afford 16.36 g of the expected crude product as a white solid.
1H-NMR (DMSO-d_6): 1.37 (s, 9H); 2.98 (m, 2H); 3.11 (m, 2H); 4.29 (t, *J* = 6.4, 1H); 4.44 (d, *J* = 6.4, 2H); 6.10 (m, 1H); 6.85 (m, 1H); 7.30-7.50 (m, 8H); 7.74 (d, *J* = 7.4, 2H); 7.90 (d, *J* = 7.4, 2H); 8.40 (s, 1H); 9.53 (br, 1H).

Preparation of N-(4-aminophenyl)({2-[(*tert*-butoxy)carbonylamino]ethyl}amino) carboxamide

[0128] Piperidine (9.68 mL, 97.75 mmol, 5.0 eq) was added at room temperature to a stirred solution of N-{4-[({2-[(*tert*-butoxy)carbonylamino]ethyl}amino)carbonylamino]phenyl} (fluo-ren-9-ylmethoxy)carboxamide (10.10 g, 19.55 mmol, 1.0 eq) in DMF (140 mL). After 2 hours stirring at room temperature, water was added to the reaction mixture and precipitation oc-cured. The resulting mixture was filtered, and the liquid phase was concentrated to afford 6.75 g of the expected product as an orange oil:
1H-NMR (DMSO-d_6) : 1.37 (s, 9H); 2.98 (m, 2H); 3.11 (m, 2H); 4.69 (s, 2H); 6.00 (t, *J* = 5.5, 1H); 6.44 (d, *J* = 8.6, 2H); 6.81 (t, *J* = 5.3, 1H); 6.97 (d, *J* = 8.6, 2H); 8.00 (s, 1H) .

Preparation of ({2-[(*tert*-butoxy)carbonylamino]ethyl}amino)-N-{4-[(2,5-dioxoazolidiny-loxy) carbonylamino]phenyl}carboxamide

[0129] *N,N*'-Disuccinimidylcarbonate (5.49 g, 21.44 mmol, 1.1 eq) was added at room temperature to a stirred solution of N-(4-aminophenyl) ({2-[(*tert*-butoxy) carbonylamino]ethyl}amino)carboxamide (6.75 g, 19.49 mmol, 1.0 eq) in CH_3CN (350 mL). After stirring overnight at room temperature, the reaction mixture was filtered and to afford 9.70 g of the expected crude product as a light brown solid.
1H-NMR (DMSO-d_6) : 1.37 (s, 9H); 2.82 (br, 4H); 2.99 (m, 2H); 3.11 (m, 2H); 6.12 (t, *J* = 5.2, 1H) ; 6.85 (t, *J* = 5.5, 1H) ; 7.27 (d, *J* = 8.9, 2H); 7. 36 (d, *J*= 8.9, 2H); 7 . 95 (s, 1H) ; 8.53 (s, 1H) .

Preparation of [(2-aminoethyl)amino]-*N*-{4-[(2,5-di-oxoazolidinyloxy) carbonylamino]phenyl}carboxamide

[0130] TFA (11.59 mL, 150.54 mmol, 5.0 eq) was added at room tem perature to a stirred suspension of ({2-[(*tert*-

butoxy)carbonylamino]ethyl}amino)-N-{4-[(2,5-dioxoazolidinyloxy)carbonylamino]phenyl}carboxamide (13.8 g, 30.11 mmol, 1.0 eq) in CH_2Cl_2 (165 mL). After stirring overnight at room temperature, solvent was evaporated and the crude product was triturated with Et_2O to afford 14.2 g of the expected crude product as a beige solid and as the trifuoroacetic acid salt.

1H-NMR (DMSO-d_6) : 2.82 (br, 4H); 2.88 (m, 2H); 3.30 (m, 2H); 6.51 (t, *J* = 5.6, 1H) ; 7.30 (d, *J* = 8.9, 2H); 7.40 (d, *J* = 8.9, 2H); 7.77 (br, 3H); 8.85 (s, 1H); 10.61 (s, 1H).

Preparation of (*1S*,*5R*)-2-[*N*-(4-{[(2-aminoethyl)amino]carbonylamino}phenyl) carbamoyl]-7-oxo-2,6-diazabicyclo[3.2.0] heptane-6-sulfonic acid (324)

[0131] (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H, 2.0 g, 10.41 mmol, 1.0 eq) was dissolved in H_2O (12.5 mL). Then CH_3CN (100 mL) was added at room temperature to the solution, followed by $NaHCO_3$ (1.57 g, 18.73 mmol, 1.8 eq) and [(2-aminoethyl)amino]-*N*-{4-[(2,5-dioxoazolidinyloxy)carbonylamino]phenyl}carboxamide (6.89 g, 14.57 mmol, 1.4 eq). After stirring overnight at room temperature, the reaction mixture was filtered to afford 3.27 g of the expected (*1S*, *5R*)-2-[*N*-(*4*-{[(2-aminoethyl)amino]carbonylamino}phenyl)carbamoyl]-7-oxo-2,6-diazabicyclo[3.2.0] heptane-6-sulfonic acid as a white solid.

1H-NMR (DMSO-d_6): 1.65 (m, 1H); 2.30 (dd, *J* = 5.8 and 13.5, 1H) ; 2.90 (m, 2H); 3.18 (m, 1H) ; 3.30 (m, 2H); 3.98 (m, 1H); 4.41 (t, *J* = 4.7, 1H); 5.22 (d, *J* = 4.3, 1H); 6.23 (t, *J* = 5.7, 1H); 7.28 (d, *J* = 8.2, 2H); 7.33 (d, *J* = 8.2, 2H); 7.65 (br, 3H); 8.38 (s, 1H); 8.53 (s, 1H).

Comparative Example 44

Sodium (1*S*,5*R*)-2-[N-(3,4-dihydroxyphenyl)carbamoyl]-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate (306)

[0132] The titled compound was prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 4-amino-1,2-benzenediol as starting materials.

1H-NMR (DMSO-d_6) : 1.64 (m, 1H); 2.29 (dd, *J* = 5.8 and 13.6, 1H); 3.13 (m, 1H); 3.93 (dd, *J* = 8.3 and 11.0, 1H); 4.37 (t, *J* = 4.8, 1H); 5.20 (d, *J* = 4.3, 1H); 6.50-6.70 (m, 2H); 6.97 (m, 1H); 7.84 and 8.15 (2s, 1H); 8.35 and 8.43 (2s, 1H); 8.77 and 8.82 (2s, 1H).

Comparative Example 45

Sodium (1*S*,5*R*)-2-{N-[3-(acetylamino)phenyl]carbamoyl}-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate (307)

[0133] The titled compound was prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 1-acetamido-3-aminobenzene as starting materials.

1H-NMR (DMSO-d_6) : 1.66 (m, 1H); 2.02 (s, 3H); 2.31 (dd, *J* = 5.8 and 13.6, 1H); 3.17 (m, 1H); 3.98 (dd, *J* = 8.3 and 11.0, 1H); 4.40 (t, *J* = 4.8, 1H); 5.27 (d, *J* = 4.3, 1H); 7.05-7.25 (m, 3H); 7.64 (m, 1H); 8.54 (s, 1H); 9.86 (s, 1H).

Comparative Example 46

Sodium (1*S*,5*R*)-7-oxo-2-[N-(3-sulfamoylphenyl)carbamoyl]-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate (308)

[0134] The titled compound was prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 3-aminobenzene sulfonamide as starting materials.

1H-NMR (DMSO-d_6) : 1.68 (m, 1H) ; 2.32 (dd, *J* = 5.8 and 13.5, 1H); 3.21 (m, 1H); 4.02 (dd, *J* = 8.5 and 11.2, 1H); 4.43 (t, *J* = 4.7, 1H); 5.28 (d, *J* = 4.2, 1H); 7.31 (br, 2H); 7.38-7.46 (m, 2H); 7.72 and 7.74 (2t, *J*= 1.9, 1H); 8.05 (t, *J* = 1.7, 1H); 8.89 (br, 1H).

Comparative Example 47

Sodium (1*S*,5*R*)-2-{N-[4-(dimethylamino)phenyl]carbamoyl}-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate (309)

[0135] The titled compound was prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 4-(dimethylamino)aniline as starting materials.
+ESI-MS spectrum: m/z: 354 $[M + H]^+$

Comparative Example 48

Sodium (1*S*,5*R*)-2-[N-(4-{N-[2-(dimethylamino)ethyl]carbamoyl}phenyl)carbamoyl]-7-oxo-2,6-diazabicyclo [3.2.0]heptane-6-sulfonate (310)

[0136] The titled compound was prepared following scheme 12 and in analogy to example 43 using (*1S*,*SR*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 4-aminobenzoic acid and 2-(dimethylamino)ethylamine as starting materials.
+ESI-MS spectrum: m/z: 425 [M+H] .

Comparative Example 49

Sodium (1*S*,5*R*)-2-(N-{4-[N-(carbamoylmethyl)carbamoyl]phenyl}carbamoyl)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate (312)

[0137] The titled compound was prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 4-aminobenzoic acid and glycinamide hydrochloride as starting materials.
1H-NMR (DMSO-d_6) : 1.68 (m, 1H) ; 2.32 (dd, *J* = 5.8 and 13.5, 1H) ; 3.21 (m, 1H) ; 3.78 (d, *J* = 5.7, 2H); 4.02 (dd, *J* = 8.3 and 11.1, 1H); 4.42 (t, *J* = 4.7, 1H); 5.28 (d, *J* = 4.6, 1H) ; 7 . 02 (br, 1H) ; 7.23 (br, 1H) ; 7.58 (d, *J* = 9.1, 2H); 7.79 (d, *J* = 9.1, 2H); 8.50 (t, *J* = 5.8, 1H); 8.78 (s, 1H).

Comparative Example 50

Sodium (1*S*,5*R*)-2-[N-(3-(1,3-oxazol-5-yl)phenyl)carbamoyl]-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate (318)

[0138] The titled compound was prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 3-(1,3-oxazol-5-yl)aniline as starting materials.
1H-NMR (DMSO-d_6) : 1.68 (m, 1H) ; 2.33 (dd, *J* = 5.8 and 13.7, 1H); 3.21 (m, 1H); 4.02 (dd, *J* = 8.1 and 11.0, 1H); 4 . 42 (t, J = 4.7, 1H) ; 5.27 (d, *J*= 4.3, 1H) ; 7.30-7.40 (m, 2H); 7.52 (m, 1H); 7.60 (s, 1H); 7.91 (s, 1H); 8.44 (s, 1H); 8.72 (br, 1H) .

Comparative Example 51

Sodium (1*S*,5*R*)-7-oxo-2-[N-(2-oxo(3-hydrobenzimidazol-5-yl))carbamoyl]-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate (319)

[0139] The titled compound was prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 5(6)-aminobenzoimidazolone as starting materials.
1H-NMR (DMSO-d_6) : 1.65 (m, 1H) ; 2.30 (dd, *J* = 5.8 and 13.5, 1H); 3.17 (m, 1H); 3.96 (dd, *J* = 8.3 and 11.0, 1H); 4.39 (t, *J* = 4.7, 1H) ; 5.22 (d, *J* = 4.3, 1H) ; 6.78 (m, 1H) ; 6.95 (m, 1H); 7.22 (m, 1H); 8.07 and 8.37 (2s, 1H); 10.34 and 10.39 (2s, 1H); 10.46 and 10.50 (2s, 1H).

Comparative Example 52

Sodium (1*S*,5*R*)-2-{N-[3-(ethoxycarbonyl)phenyl]carbamoyl}-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate (320)

[0140] The titled compound was prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 3-aminobenzoic acid ethyl ester as starting materials.
1H-NMR (DMSO-d_6) : 1.32 (t, *J* = 7.1, 3H); 1.68 (m, 1H) ; 2.32 (dd, *J* = 5.8 and 13.5, 1H); 3.20 (m, 1H); 4.02 (dd, *J* = 8.3 and 11.0, 1H); 4.31 (q, *J* = 7.1, 2H); 4.42 (t, *J* = 4.7, 1H); 5.27 (d, *J* = 4.5, 1H); 7.39 (t, *J* = 8.0, 1H); 7.56 (2dd, *J* = 1.2 and 1.6, 1H); 7.82 (m, 1H); 8.14(t, *J* = 1.9, 1H); 8.81 (br, 1H) .

Comparative Example 53

Sodium (1*S*,5*R*)-2-{N-[3-(hydroxymethyl)phenyl]carbamoyl}-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate (321)

[0141] The titled compound was prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 3-(hydroxymethyl)aniline as starting materials.
[0142] 1H-NMR (DMSO-d_6) : 1.67 (m, 1H) ; 2.31 (dd, *J* = 5.8 and 13.5, 1H); 3.18 (m, 1H); 3.99 (dd, *J* = 8.3 and 11.4, 1H); 4.41 (t, *J* = 4.7, 1H); 4.45 (d, *J* = 5.8, 2H); 5.15 (t, *J* = 5.6, 1H) ; 5.27 (d, *J* = 4.3, 1H) ; 6.90 (m, 1H) ; 7.18 (t, *J* = 7.8, 1H); 7.39 (m, 1H); 7.45 (m, 1H); 8.52 (br, 1H).

Comparative Example 54

(1*S*,5*R*)-2-N-[4-({[2-(2-aminoethoxy)ethyl]amino}carbonylamino)phenyl] carbamoyl}-7-oxo-2,6-diazabicyclo [3.2.0]heptane-6-sulfonic acid (323)

[0143] The titled compound was prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 1,4-benzene diamine and 2,2-oxydiethylamine dihydrochloride (Eur. J. Org. Chem. 2002, 3004) as starting materials.
1H-NMR (DMSO-d_6): 1.65 (m, 1H); 2.30 (dd, *J* = 5.8 and 13.5, 1H); 2.99 (m, 2H); 3.16 (m, 1H); 3.29 (m, 2H); 3.49 (t, *J* = 5.7, 2H); 3.60 (t, *J* = 5.2, 2H); 3.95 (m, 1H); 4.39 (t, *J* = 4.7, 1H) ; 5.20 (d, *J* = 4.3, 1H) ; 6.13 (t, *J* = 5.7, 1H) ; 7.24 (d, *J* = 8.2, 2H); 7.31 (d, *J* = 8.2, 2H); 7.73 (br, 3H); 8.35 (s, 1H); 8.37 (s, 1H).

Comparative Example 55

(1*S*,5*R*)-7-oxo-2-(N-{4-[(4-piperidylamino)carbonylamino]phenyl}carbamoyl)-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (325)

[0144] The titled compound was prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 1,4-benzene diamine and 1-BOC-4-amino-piperidine hydrochloride as starting materials.
1H-NMR (DMSO-d_6) : 1.52 (m, 2H); 1.68 (m, 1H) ; 1.98 (m, 2H); 2.31 (dd, *J* = 6.0 and 13.6, 1H); 3.00 (m, 2H); 3.17 (m, 1H); 3.23 (m, 3H); 3.72 (m, 1H); 3.97 (dd, *J* = 8.3 and 11.0, 1H); 4.40 (t, *J* = 4.8, 1H); 5.21 (d, *J* = 4.2, 1H); 6.28 (d, *J* = 7.5, 1H); 7.23 (d, *J* = 9.2, 2H); 7.32 (d, *J* = 9.2, 2H); 8.12 (s, 1H) ; 8.28 (br, 1H) ; 8.38 (s, 1H) .

Comparative Example 56

(1*S*,5*R*)-7-oxo-2-{N-[4-(piperazinylcarbonylamino)phenyl]carbamoyl}-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (326)

[0145] The titled compound was prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 1,4-benzene diamine and 1-BOC-piperazine as starting materials.
1H-NMR (DMSO-d_6) : 1.65 (m, 1H) ; 2.32 (dd, *J* = 5.7 and 13.6, 1H); 3.13 (m, 4H); 3.19 (m, 1H); 3.62 (m, 4H); 3.97 (dd, *J* = 8.3 and 11.2, 1H); 4.40 (t, *J* = 4.7, 1H); 5.31 (d, *J* = 4.3, 1H); 7.28 (d, *J* = 9.2, 2H); 7.36 (d, *J* = 9.2, 2H); 8.42 (s, 1H);

8.58 (s, 1H); 8.63 (br, 1H).

Comparative Example 57

Sodium (1*S*,5*R*)-2-[N-(4-aminophenyl)carbamoyl]-7-oxo-2,6-diazabicyclo[3.2.0] heptane-6-sulfonate (327)

[0146] The titled compound was prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available N-BOC-1,4-phenylene diamine as starting materials.
+ESI-MS spectrum: m/z: 326 $[M + H]^+$.

Comparative Example 58

Sodium (1*S*,5*R*)-2-[N-(2-carbamoylphenyl)carbamoyl]-7-oxo-2,6-diazabicyclo[3.2.0] heptane-6-sulfonate (328)

[0147] The titled compound was prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 2-aminobenzamide as starting materials.
1H-NMR (DMSO-d_6) : 1.67 (m, 1H) ; 2.36 (dd, *J* = 6.0 and 13.8, 1H); 3.23 (m, 1H); 3.97 (m, 1H); 4.42 (t, *J* = 4.7, 1H); 5.24 (d, *J* = 4.2, 1H); 7.00 (m, 1H); 7.45 (m, 1H); 7.72 (br, 1H); 7.79 (dd, *J* = 1.2 and 7.9, 1H); 7.91 (s, 1H); 8.28 (br, 1H) ; 8.37 (dd, *J* = 1.2 and 8.4, 1H) .

Comparative Example 59

Sodium (1*S*,S*R*)-7-oxo-2-[N-(4-{2-[(phenylmethoxy)carbonylamino]acetylamino}phenyl)carbamoyl]-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate (329)

[0148] The titled compound was prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 1,4-benzene diamine and N-carbobenzoxyglycine as starting materials.
1H-NMR (DMSO-d_6) : 1.66 (m, 1H) ; 2.31 (m, 1H) ; 3.18 (m, 1H); 3.78 (d, *J* = 6.1, 2H); 3.98 (dd, *J* = 8.0 and 11.1, 1H); 4.40 (t, *J* = 4.8, 1H); 5.03 (s, 2H); 5.23 (d, *J* = 4.5, 1H); 7.22-7.58 (m, 10H); 8.49 (s, 1H) ; 9.83 (s, 1H) .

Comparative Example 60

(1*S*,5*R*)-2-[N-(4-{[(2-morpholin-4-ylethyl)amino]carbonylamino}phenyl)carbamoyl]-7-oxo-2,6-diazabicyclo [3.2.0] heptane-6-sulfonic acid (330)

[0149] The titled compound was prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 1,4-benzene diamine and N-(2-aminoethyl)morpholine as starting materials.
^{1}H-NMR (DMSO-d_6): 1.67 (m, 1H); 2.31 (dd, *J* = 6.1 and 13.7, 1H); 3.00-3.25 (m, 5H); 3.40-3.75 (m, 6H); 3.97 (m, 3H); 4.41 (t, *J* = 4.7, 1H) ; 5.22 (d, *J* = 4.2, 1H) ; 6.28 (br, 1H); 7.28 (d, *J* = 9.2, 2H); 7.33 (d, *J* = 9.2, 2H); 8.39 (s, 1H); 8.50 (s, 1H); 9.47 (br, 1H).

Comparative Example 61

(1*S*,5*R*)-2-[N-(4-{[(2-{[(2-morpholin-4-ylethyl)amino]carbonylamino}ethyl)amino]carbonylamino}phenyl) carbamoyl]-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (331)

[0150] The titled compound was prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 1,4-benzene diamine, N-(2-aminoethyl)morpholine and ethylenediamine as starting materials.
^{1}H-NMR (DMSO-d_6) : 1.66 (m, 1H); 2.31 (dd, *J* = 6.1 and 13.7, 1H); 3.00-3.22 (m, 11H); 3.49 (m, 2H); 3.61 (m, 2H); 3.96 (m, 3H); 4.39 (t, *J* = 4.7, 1H); 5.22 (d, *J* = 4.5, 1H); 6.11 (t, *J* = 5.8, 1H); 6.32 (m, 2H); 7.24 (d, *J* = 9.1, 2H); 7.33 (d, *J* = 9.1, 2H); 8.38 (d, *J* = 4.4, 1H); 9.53 (br, 1H).

Comparative Example 62

(1*S*,5*R*)-2-(N-{4-[N-(2-aminoethyl)carbamoyl]phenyl}carbamoyl)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (332)

[0151] The titled compound was prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 4-aminobenzamide and 2-bromo-ethanamine as starting materials.
1H-NMR (DMSO-d_6): 1.69 (m, 1H); 2.33 (dd, *J* = 5.8 and 13.7, 1H) ; 2.97 (m, 2H); 3.22 (m, 1H) ; 3.48 (m, 2H); 4.01 (dd, *J* = 8.2 and 11.0, 1H); 4.43 (t, *J* = 4.7, 1H); 5.27 (d, *J* = 4.5, 1H); 7.61 (d, *J* = 9.1, 2H); 7.75 (m, 5H); 8.43 (m, 1H); 8.81 (s, 1H).

Comparative Example 63

Sodium (1*S*,5*R*)-2-(N-{4-[(tert-butoxy)carbonylamino]phenyl}carbamoyl)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate (333)

[0152] The titled compound was prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available N-BOC-1,4-benzene diamine as starting materials.
1H-NMR (DMSO-d_6) : 1.46 (s, 9H); 1.64 (m, 1H) ; 2.30 (dd, *J* = 5.8 and 13.5, 1H); 3.16 (m, 1H); 3.97 (dd, *J* = 8.5 and 11.3, 1H); 4.39 (t, *J* = 4.8, 1H); 5.22 (d, *J* = 4.3, 1H); 7.25-7.35 (m, 4H); 8.41 (s, 1H) ; 9.17 (s, 1H) .

Comparative Example 64

Sodium (1*S*,5*R*)-2-{N-[(3,4-dihydroxyphenyl)methyl]carbamoyl}-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate (303)

[0153] The titled compound was prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and commercially available 3,4-dihydroxybenzylamine.
-ESI-MS spectrum: m/z: 356 $[M - H]^+$.

Comparative Example 65

(1*S*,5*R*)-2-{*N*-[4-(morpholin-4-ylmethyl)phenyl]carbamoyl)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (334).

[0154] The titled compound has been prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 4-(morpholinomethyl) aniline as starting materials.
1H-NMR (DMSO-d_6) : 1.67 (m, 1H); 2.30 (dd, *J* = 5.8 and 13.6, 1H); 3.12 (m, 2H); 3.25 (m, 3H); 3.60 (t, *J* = 11.8, 2H); 3.97 (m, 3H); 4.26 (br, 2H); 4.42 (t, *J* = 4.7, 1H); 5.25 (d, *J* = 4.3, 1H); 7.36 (d, *J* = 8.2, 2H); 7.60 (d, *J* = 8.2, 2H); 8.74 (br, 1H); 9.61 (br, 1H).

Comparative Example 66

(1*S*,5*R*)-2-[*N*-(4-morpholin-4-ylphenyl)carbamoyl]-7-oxo-2,6-diazabicyclo [3.2.0]heptane-6-sulfonic acid (335)

[0155] The titled compound has been prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 4-morpholinoaniline as starting materials.
1H-NMR (DMSO-d_6): 1.67 (m, 1H); 2.32 (dd, *J* = 5.8 and 13.6, 1H); 3.19 (m, 1H); 3.32 (br, 4H); 3.85 (br, 4H); 3.98 (m, 1H); 4.42 (t, *J* = 4.7, 1H); 5.25 (d, *J* = 4.3, 1H); 7.24 (br, 2H); 7.50 (d, *J* = 8 . 6, 2H); 8.60 (br, 1H) .

Comparative Example 67

(1*S*,5*R*)-2-[*N*-(3-morpholin-4-ylphenyl)carbamoyl]-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (336).

[0156] The titled compound has been prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-

oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 3-morpholino-4-ylaniline as starting materials.
1H-NMR (DMSO-d_6): 1.67 (m, 1H); 2.32 (dd, *J* = 5.8 and 13.6, 1H); 3.19 (m, 1H); 3.26 (br, 4H); 3.82 (br, 4H); 3.99 (m, 1H); 4.42 (t, *J* = 4.7, 1H); 5.25 (d, *J* = 4.3, 1H); 6.84 (d, *J* = 7.5, 1H); 7.15 (d, *J* = 8.1, 1H); 7.23 (t, *J* = 8.1, 1H) ; 7.48 (br, 1H) ; 8.60 (br, 1H).

Comparative Example 68

(1*S*,5*R*)-7-oxo-2-{*N*-[3-(piperazinylmethyl)phenyl]carbamoyl}-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (337).

[0157] The titled compound has been prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available *tert*-butyl 4-(3-aminobenzyl)piperazine-1-carboxylate as starting materials. The final deprotection step, using trifluoroacetic acid, has been performed in analogy to example 1.
1H-NMR (DMSO-d_6): 1.67 (m, 1H); 2.32 (dd, *J* = 5.8 and 13.6, 1H); 2.58 (br, 4H); 3.09 (br, 4H); 3.19 (m, 1H); 3.49 (br, 2H); 3.98 (m, 1H); 4.41 (t, *J* = 4.7, 1H); 5.25 (d, *J* = 4.3, 1H); 6.89 (d, *J* = 7.5, 1H); 7.21 (t, *J* = 8.1, 1H); 7.37 (t, *J* = 8.1, 1H); 7.52 (br, 1H); 8.44 (br, 2H); 8.55 (br, 1H).

Comparative Example 69

2-[*N*-((3*S*)pyrrolidin-3-yl)carbamoyl](1*S*,5*R*)-7-oxo-2,6-diazabicyclo [3.2.0]heptane-6-sulfonic acid (338).

[0158] The titled compound has been prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and commercially available (S)-3-amino-1-N-BOC-pyrrolidine as starting materials. The final deprotetion step, using trifluoroacetic acid, has been performed in analogy to example 1.
+ESI-MS spectrum: m/z: 305 $[M+H]^+$.

Comparative Example 70

2-[N-(4-{[((3*S*)pyrrolidin-3-yl)amino]carbonylamino}phenyl)carbamoyl](1*S*,5*R*)-7-oxo-2,6-diazabicyclo[3.2.0] heptane-6-sulfonic acid (339).

[0159] The titled compound has been prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 1,4-benzene diamine and also commercially available (S)-3-amino-1-N-BOC-pyrrolidine as starting materials. The final deprotetion step, using trifluoroacetic acid, has been performed in analogy to example 1.
1H-NMR (DMSO-d_6): 1.65 (m, 1H); 1.82 (m, 1H); 2.17 (m, 1H) ; 2.31 (dd, *J* = 5.8 and 13.6, 1H) ; 3.06 (dd, *J* = 5.1 and 11.8, 1H); 3.19 (m, 2H); 3.29 (m, 2H); 3.96 (dd, *J* = 8.3 and 11.1, 1H) ; 4.22 (m, 1H) ; 4.40 (t, *J* = 4.7, 1H) ; 5.22 (d, *J* = 4.3, 1H); 6.40 (d, *J* = 6.0, 1H); 7.26 (d, *J* = 9.2, 2H); 7.33 (d, *J* = 9.2, 2H); 8.37 (s, 1H); 8.41 (s, 1H); 8.70 (br, 2H).

Comparative Example 71

(1S,5R)-2-{*N*-[4-(2-morpholin-4-ylethoxy)phenyl]carbamoyl}-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (340).

[0160] The titled compound has been prepared following scheme 12 and in analogy to example 43 using (1*S*,5*R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 4-(2-morpholin-4-ylethoxy)aniline as starting materials.
1H-NMR (DMSO-d_6): 1.66 (m, 1H); 2.31 (dd, *J* = 5.8 and 13.6, 1H); 3.18 (m, 3H); 3.54 (m, 4H); 3.70 (m, 2H); 3.96 (m, 3H); 4.29 (m, 2H); 4.41 (t, *J* = 4.7, 1H) ; 5.21 (d, *J* = 4.3, 1H); 6.93 (d, *J* = 9.0, 2H); 7.41 (d, *J* = 9.0, 2H); 8.44 (s, 1H); 9.81 (br, 1H).

Comparative Example 72

(1*S*,5*R*)-2-{*N*-[3-(2-morpholin-4-ylethoxy)phenyl]carbamoyl}-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (341).

[0161] The titled compound has been prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 3-(2-morpholin-4-ylethoxy)aniline as starting materials.
1H-NMR (DMSO-d_6): 1.66 (m, 1H); 2.31 (dd, *J* = 5.8 and 13.6, 1H) ; 3.18 (m, 3H); 3.54 (m, 4H); 3.70 (m, 2H); 3.98 (m, 3H); 4.29 (m, 2H); 4.41 (t, *J* = 4.7, 1H); 5.23 (d, *J* = 4.3, 1H) ; 6.61 (dd, *J* = 1.9 and 8.1, 1H) ; 7.04 (dd, *J* = 1.1 and 8.1, 1H) ; 7.19 (t, *J* = 8.1, 1H) ; 7.38 (s, 1H) ; 8.57 (s, 1H) ; 9.81 (br, 1H).

Comparative Example 73

(1*S*,5*R*)-7-oxo-2-[*N*-(4-piperidylphenyl)carbamoyl]-2,6-diazabicyclo [3.2.0]heptane-6-sulfonic acid (342).

[0162] The titled compound has been prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 4-(1-piperidino)aniline as starting materials.
1H-NMR (DMSO-d_6): 1.40-2.00 (m, 7H); 2.30 (dd, *J* = 5.8 and 13.5, 1H) ; 3.22 (m, 1H) ; 3.45 (br, 4H); 3.98 (dd, *J* = 8.3 and 11.0, 1H); 4.42 (t, *J* = 4.7, 1H); 5.24 (d, *J* = 4.3, 1H); 7.50-7.75 (m, 4H); 8.85 (br, 1H) ; 10.80 (s, 1H).

Comparative Example 74

(1S,5R)-2-[N-(6-morpholin-4-yl(3-pyridyl))carbamoyl]-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (343).

[0163] The titled compound has been prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 6-morpholinopyridine-3-amine as starting materials.
1H-NMR (DMSO-d_6): 1.70 (m, 1H); 2.34 (dd, *J* = 5.8 and 13.5, 1H); 3.22 (m, 1H); 3.54 (m, 4H); 3.76 (m, 4H); 3.98 (dd, *J* = 8.3 and 11.0, 1H); 4.42 (t, *J* = 4.7, 1H); 5.19 (d, *J* = 4.4, 1H); 7.38 (d, *J* = 9.7, 1H); 8.06 (dd, *J* = 2.4 and 9.7, 1H) ; 8.29 (d, *J* = 2.4, 1H); 8.88 (br, 1H).

Comparative Example 75

(1*S*,5*R*)-2-{*N*-[4-(4-methylpiperazinyl)phenyl]carbamoyl}-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (344).

[0164] The titled compound has been prepared following scheme 12 and in analogy to example 43 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and the commercially available 4-(4-methylpiperazino) aniline as starting materials.
1H-NMR (DMSO-d_6) : 1.65 (m, 1H); 2.31 (dd, *J* = 5.8 and 13.6, 1H); 2.69 (m, 2H); 2.99 (m, 2H); 3.05-3.25 (m, 8H); 3.96 (dd, *J* = 8.3 and 11.0, 1H); 4.39 (t, *J* = 4.7, 1H); 5.31 (d, *J* = 4.3, 1H); 6.91 (d, *J* = 9.0, 2H); 7.35 (d, *J* = 9.0, 2H); 8.36 (s, 1H).

Comparative Example 76

(1S,5R)-2-{2-[1-(dimethylamino)-2-oxohydropyrimidin-4-ylthio]acetyl}-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (203)

[0165] The titled compound was prepared following scheme 12 in analogy to example 14 using (5S,1R)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound E) and 2-[1-(dimethylamino)-2-oxohydropyrimidin-4-ylthio]acetic acid. The resulting compound was then sulfonated according to the procedure described in J. Org. Chem. 1982, 5160.
+ESI-MS spectrum: m/z: 404 $[M+H]^+$.

[0166] 2-[1-(dimethylamino)-2-oxohydropyrimidin-4-ylthio]acetic acid was prepared from the 3-(dimethylamino)-6-sulfanyl-3-hydropyrimidin-2-one (US-A-4,348,518) and bromoacetic acid according to the procedures described in Russian J. Org. Chem. 2000, 761.

Comparative Example 77

(1*S*,5*R*)-7-oxo-2-{2-[4-(2-pyridiniumacetylamino)phenylthio]acetyl}-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate, inner salt (204)

[0167] The titled compound was prepared following scheme 13 in analogy to example 14 using (5*S*,1*R*)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound E) and the 2-[4-(2-pyridylacetylamino)phenylthio]acetic acid as starting materials. The resulting compound was then sulfonated according to the procedure described in J. Org. Chem. 1982, 5160.
+ESI-MS spectrum: m/z: 397 $[M+H-SO_3]^+$.

Comparative Example 78

(1*S*,5*R*)-2-(2-{1-[2-(dimethylamino)ethyl](1,2,3,4-tetraazol-5-ylthio)}acetyl)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (205)

[0168] The titled compound was prepared following scheme 13 in analogy to example 14 using (*5*S,1*R*)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound E) and 2-{1-[2-(dimethylamino)ethyl]-1,2,3,4-tetraazol-5-ylthio}acetic acid as starting materials. The resulting compound was then sulfonated according to the procedure described in J. Org. Chem. 1982, 5160.

[0169] 2-{1-[2-(dimethylamino)ethyl]-1,2,3,4-tetraazol-5-ylthio}acetic acid was prepared from commercially available1-(2-dimethylaminoethyl)-5-mercapto-1,2,3,4-tetrazole and bromo acetic acid according to the procedures described in Russian J. Org. Chem. 2000, 761
+ESI-MS spectrum: m/z: 406 $[M+H]^+$.

Comparative Example 79

Sodium (1*S*,5*R*)-2-[2-(1-methyl(1,3,4-thiadiazol-2-ylthio))acetyl]-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate (202)

[0170] The titled compound was prepared following scheme 13 in analogy to example 14 using (5*S*,1*R*)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound E) and the commercially available 2-(5-methyl-1,3,4-thiadiazol-2-ylthio)acetic acid as starting materials. The resulting compound was then sulfonated according to the procedure described in J. Org. Chem. 1982, 5160.
-ESI-MS spectrum: m/z: 363 $[M - H]^+$.

Comparative Example 80

(1*S*,5*R*)-2-[2-(4-{*N*-[2-(dimethylamino)ethyl]carbamoyl}phenylthio)acetyl]-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (207).

[5-(2-Dimethylamino-ethylcarbamoyl)phenylthio]acetic acid

[0171] To a suspension of commercially available 4-mercapto benzoic acid (1.54 g, 10 mmol) in water was added NaOH (0.88 g, 22 mmol). The resulting solution was stirred at room temperature for 30 min and then bromo acetic acid ethyl ester (1.67 g, 10 mmol) was slowly added to the previous solution. After stirring at room temperature for 2 hours, an aqueous solution containing HCl (1M) was added. The obtained precipitate was filtrated, washed with water and dried to afford 1.5g of 4-ethoxycarbonylmethylthio benzoic acid.
-ESI-MS spectrum: m/z: 239 $[M-H]^+$.

[0172] Then the corresponding acid chloride of 4-ethoxycarbonylmethylthio benzoic acid was prepared in analogy to the procedure described in Synthesis, 1985, 517 and the condensation of the commercially available 2-dimethylaminoethyl amine and the hydrolysis of the ester group were performed in analogy to the procedure described in Bioorg. Med. Chem. Lett. 2003, 1517.
+ESI-MS spectrum: m/z: 283 $[M+H]^+$.

(1*S*,5*R*)-2-[2-(4-{*N*-[2-(dimethylamino)ethyl]carbamoyl}phenylthio)acetyl]-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (207).

[0173] [5-(2-Dimethylamino-ethylcarbamoyl)phenylthio]acetic acid (144 mg, 0.49 mmol, 1.0 eq) was added at room

temperature to a stirred solution of (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H, 100 mg, 0.49 mmol, 1.0 eq) in DMSO (4 mL), followed by O-(benzotriazo-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) (225 mg, 0.59 mmol, 1.2 eq) and triethylamine (83 μL, 0.59 mmol, 1.2 eq). After 4 hours stirring at room temperature, DMSO was evaporated, the crude was treated with acetonitrile. The resulting mixture was filtered to afford the crude product as a yellow solid which was purified by preparative HPLC: 74 mg (30%).
_1H-NMR (DMSO-d_6): 1.70 (m, 1H); 2.32 (m, 1H); 2.83 (s, 6H); 3.14 and 3.38 (2m, 1H); 3.26 (m, 2H); 3.57 (m, 2H); 3.96-4.23 (m, 3H); 4.34 and 4.51 (2t, *J* = 4.7, 1H); 5.16 and 5.31 (2d, *J* = 4.3, 1H); 7.43 (dd, *J* = 8.5 and 12.6, 2H); 7.78 (dd, *J* = 2.4 and 8.5, 2H); 8.62 (m, 1H) ; 9.18 (br, 1H).

Comparative Example 81

(1*S*,5*R*)-2-[2-(5-{*N*-[2-(dimethylamino)ethyl]carbamoyl}(2-pyridylthio)) acetyl]-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (208).

[0174] The titled compound has been prepared following scheme 13 and in analogy to example 80 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and [5-(2-dimethylaminoethylcarbamoyl)pyridin-2-ylthio]acetic acid as starting materials.
1H-NMR (DMSO-d_6): 1.66 (m, 1H); 2.33 (m, 1H); 2.82 (s, 3H); 2.85 (s, 3H); 3.15 and 3.48 (2m, 1H); 3.26 (m, 2H); 3.61 (m, 2H); 3.98-4.55 (m, 4H); 5.16 and 5.35 (2t, *J* = 4.3, 1H) ; 7.48 (d, *J* = 8.4, 1H) ; 8.02 (m, 1H) ; 8.75 (m, 1H) ; 8.85 (dd, *J* = 1.8 and 7.5, 1H) ; 9.16 (br, 1H).
[0175] [5-(2-Dimethylamino-ethylcarbamoyl)pyridin-2-ylthio]acetic acid was prepared in analogy to the procedure described in Bioorg. Med. Chem. Lett. 2003, 1517 using bromo acetic acid ethyl ester and commercially available 2-dimethylaminoethyl amine.

Comparative Example 82

(1*S*,5*R*)-2- (2-{4-[*N*-(2-aminoethyl)carbamoyl]phenylthio}acetyl)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (209).

[0176] The titled compound has been prepared following scheme 13 and in analogy to example 80 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and [4-(2-*tert*-butoxycarbonylaminoethylcarbamoyl) phenylthio]acetic acid as starting materials. The final deprotection step, using trifluoroacetic acid, has been performed in analogy to example 1.
1H-NMR (DMSO-d_6): 1.72 (m, 1H); 2.33 (m, 1H); 2.97 (t, *J* = 6.0, 2H); 3.14 and 3.38 (2m, 1H); 3.48 (q, *J* = 6.0, 2H); 3.95-4.24 (m, 3H); 4.34 and 4.51 (2t, *J* = 4.8, 1H) ; 5.17 and 5.32 (2d, *J* = 4.3, 1H); 7.42 (dd, *J* = 8.5 and 13.1, 2H); 7.78 (dd, *J* = 2.5 and 8.5, 2H); 8.55 (m, 1H).
[0177] [4-(2-*Tert*-butoxycarbonylaminoethylcarbamoyl)phenylthio]acetic acid was prepared in analogy to the procedure described in example 80 using 4-ethoxycarbonylmethylthiobenzoic acid and commercially available (2-aminoethyl) carbamic acid *tert*-butyl ester.

Comparative Example 83

(1*S*,5*R*)-2-(2-{4-[*N*-(2-aminoethyl)-*N*-methylcarbamoyl]phenylthio}acetyl)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (210).

[0178] The titled compound has been prepared following scheme 13 and in analogy to example 80 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and {4-[(2-*tert*-butoxycarbonylaminoethyl)methylcarbamoyl]phenylthio}acetic acid as starting materials. The final deprotection step, using trifluoroacetic acid, has been performed in analogy to example 1.
-ESI-MS spectrum: m/z: 441 $[M-H]^+$
[0179] {4-[(2-*Tert*-butoxycarbonylaminoethyl)methylcarbamoyl]phenylthio}acetic acid was prepared in analogy to the procedure described in example 80 using 4-ethoxycarbonylmethylsulfanylbenzoic acid and commercially available (2-methylamino-ethyl)carbamic acid tert-butyl ester.

Comparative Example 84

(1*S*,5*R*)-2-[2-(4-{*N*-[2-(methylamino)ethyl]carbamoyl}phenylthio)acetyl]-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (211)

[0180] The titled compound has been prepared following scheme 13 and in analogy to example 80 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and {4-[2-(*tert*-butoxycarbonylmethylamino)ethylcarbamoyl] phenyl-thio}acetic acid as starting materials. The final deprotection step, using trifluoroacetic acid, has been performed in analogy to example 1.
-ESI-MS spectrum: m/z: 441 $[M-H]^+$

[0181] {4-[2-(*Tert*-butoxycarbonylmethylamino)ethylcarbamoyl]phenylthio}acetic acid was prepared in analogy to the procedure described in example 80 using 4-ethoxycarbonyl methylthiobenzoic acid and commercially available (2-aminoethyl)methylcarbamic acid tert-butyl ester.

Comparative Example 85

(1S,5R)-7-oxo-2-{2-[4-(piperazinylcarbonyl)phenylthio]acetyl}-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid **(212).**

[0182] The titled compound has been prepared following scheme 13 and in analogy to example 80 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and 4-(4-carboxymethylthiobenzoyl)piperazine-1-carboxylic acid *tert*-butyl ester as starting materials. The final deprotection step, using trifluoroacetic acid, has been performed in analogy to example 1.
-ESI-MS spectrum: m/z: 453 $[M-H]^+$

[0183] 4-(4-Carboxymethylsulfanyl-benzoyl)piperazine-1-carboxylic acid *tert*-butyl ester was prepared in analogy to the procedure described in example 80 using 4-ethoxycarbonylmethylthiobenzoic acid and commercially available piperazine-1-carboxylic acid *tert*-butyl ester.

Comparative Example 86

(1*S*,5*R*)-2-{2-[4-(2-aminoethoxy)phenylthio]acetyl}-7-oxo-2,6-diazabicyclo [3.2.0]heptane-6-sulfonic acid (213).

[0184] The titled compound has been prepared following scheme 13 and in analogy to example 80 using (*1S*,*5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and [4-(2-*tert*-butoxycarbonylaminoethoxy)phenylthio]acetic acid as starting materials. The final deprotection step, using trifluoroacetic acid, has been performed in analogy to example 1.
-ESI-MS spectrum: m/z: 400 $[M-H]^+$

[0185] [4-(2-*Tert*-butoxycarbonylaminoethoxy)phenylthio]acetic acid was prepared in analogy to the procedure described in J. Med Chem.2000, 721 using first bromo acetic ethyl ester and then the commercially available (2-bromoethyl) carbamic acid tert-butyl ester.

Comparative Example 87

(1*S*,5*R*)-2-(2-{5-[*N*-(2-aminoethyl)carbamoyl](2-pyridylthio)}acetyl)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (214).

[0186] The titled compound has been prepared following scheme 13 and in analogy to example 80 using (*1S,5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and [4-(2-tert-butoxycarbonylaminoethylcarbamoyl) phenylthio]acetic acid as starting materials. The final deprotection step, using trifluoroacetic acid, has been performed in analogy to example 1.
-ESI-MS spectrum: m/z: 428 $[M-H]^+$

[0187] [4-(2-*Tert*-butoxycarbonylamino-ethylcarbamoyl)-phenylthio]acetic acid was prepared in analogy to the procedure described in Bioorg. Med. Chem. Lett. 2003, 1517 using bromo acetic acid ethyl ester and commercially available (2-aminoethyl)carbamic acid *tert*-butyl ester.

Comparative Example 88

(1*S*,5*R*)-2-[2-(5-{*N*-[2-(methylamino)ethyl]carbamoyl}(2-pyridylthio))acetyl]-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (215).

[0188] The titled compound has been prepared following scheme 13 and in analogy to example 80 using (*1S,5R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (compound H) and {4-[2-(*tert*-butoxycarbonylmethylamino)ethylcarbamoyl]phenylthio} acetic acid as starting materials. The final deprotection step, using trifluoroacetic acid, has been performed in analogy to example 1.
-ESI-MS spectrum: m/z: 442 $[M-H]^+$

[0189] {4-[2-(*Tert*-butoxycarbonylmethylamino)ethylcarbamoyl]phenylthio}acetic acid was prepared in analogy to the procedure described in Bioorg. Med. Chem. Lett. 2003, 1517 using bromo acetic acid ethyl ester and commercially available (2-methylaminoethyl)carbamic acid tert-butyl ester.

Comparative Example 89

(1*S*,5*R*)-2-{2-[(3-carbamoylpyridyl-4)carbonylamino]acetyl}-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (402)

[0190] The titled compound was prepared following scheme 11 in analogy to example 24 using (5*S*,1*R*)-4-(2-bromoacetyl)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound F) which was first sulfonated (J. Org. Chem. 1982, 5160) and the commercially available 3,4-pyridine dicarboxamide as starting materials.
+ESI-MS spectrum: m/z: 398 $[M+H]^+$

Comparative Example 90

Sodium 2-{[(4*S*)-2-(2-hydroxyphenyl)(4,5-dihydro-1,3-thiazolin-4-yl)]carbonyl}(1*S*,5*R*)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate (404)

[0191] The titled compound was prepared following scheme 13 in analogy to example 14 using (5*S*,1*R*)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound E) and the (4*S*) 4,5-dihydro-2-(2-hydroxyphenyl)-4-thiazolecarboxylic acid (JP59141554). The resulting compound was then sulfonated according to the procedure described in J. Org. Chem. 1982, 5160.
-ESI-MS spectrum: m/z: 397 $[M+H]^+$.

Comparative Example 91

Sodium (1S,5R)-2-{2-[(5-fluoro-2-oxohydropyrimidin-4-yl)amino]acetyl}-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate (405)

[0192] The titled compound was prepared following scheme 11 in analogy to example 22 using (5*S*,1*R*)-4-(2-bromoacetyl)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound F) and the commercially available 4-amino-5-fluoro pyridine-2-one.
-ESI-MS spectrum: m/z: 361 $[M+H]^+$.

Comparative Example 92

(1*S*,5*R*)-2-[2-amino-2-(4-carbamoylphenyl)acetyl]-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonic acid (406)

[0193] The titled compound was prepared following scheme 13 in analogy to example 14 using (5*S*,1*R*)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound E) and 2-amino-2-(4carbamoylphenyl) acetic acid, obtained according to the procedure described in Eur. J. Med. Chem. 2003, 289 from 4-{[(tert-butoxy)carbonylamino](methoxycarbonyl) methyl}benzoic acid (WO-A-2000/076970). The resulting compound was then sulfonated according to the procedure described in J. Org. Chem. 1982, 5160.
+ESI-MS spectrum: m/z: 368 $[M+H]^+$.

Comparative Example 93

(1*S*,5*R*)-2-{2-[4-(imidazolylcarbonyl)-1-methylpiperazinium]acetyl}-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate, inner salt (407)

[0194] The titled compound was prepared following scheme 13 in analogy to example 24 using (5*S*,1*R*)-4-(2-bromoacetyl)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound F) and 1-(1H-imidazol-1-ylcarbonyl)-4-methyl-piperazine (Ind. J. Chem., Section B, 1987, 748).
+ESI-MS spectrum: m/z: 426 $[M]^+$.

Comparative Example 94

Sodium (1*S*,5*R*)-2-{[(4-carbamoylphenyl)amino]carbonylamino}-7-oxo-2,6-diazabicyclo[3.2.0]heptane-6-sulfonate (408)

[0195] The titled compound was prepared following the procedure described for example 18 of US-B-6,566,355 using (5*S*,1*R*)-4,7-diazabicyclo[3.2.0]heptan-6-one (compound E) and 4-[(3-phenyl-1,2-oxaziridin-2-yl)carbonylamino]benzamide. The resulting compound was then sulfonated according to the procedure described in J. Org. Chem. 1982, 5160.
-ESI-MS spectrum: m/z: 369 $[M+H]^+$

BIOLOGICAL EVALUATION

[0196] Antimicrobial activity of the compounds of above formula I and of their combinations was determined against a selection of organisms according to the standard procedures described by the National Committee for Clinical Laboratory Standards (National Committee for Clinical Laboratory Standards (2000). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically-Fifth Edition: Approved Standard M7-A5. NCCLS, Wayne, PA, USA).

[0197] The compounds to be tested were dissolved in 100% DMSO or sterile broth according to their aqueous solubility and were diluted to the final reaction concentration (0.06 - 32 μg/mL) in microbial growth media (IsoSensiTest Broth + 16 μg/mL 2,2'-bipyridyl). In all cases the final concentration of DMSO incubated with the bacteria is less than or equal to 1%. For estimation of the minimal inhibitory concentrations (MIC), 2-fold dilutions of compounds were added to wells of a microtitre plate containing 10^6 bacteria/mL. Plates were incubated overnight at an appropriate temperature (30°C or 37°C) and optical densities assessed by eye. The MIC value is defined as the lowest compound concentration completely inhibiting visible growth of the test organism. When combinations between the compounds of above formula I with β-lactamase inhibitors of formula II and III-XIII are evaluated the compounds of above formula I are tested in dilution series as described above while the β-lactamase inhibitors of formula II and III-XIII were present in all wells at a constant concentration of 4 μg/mL each.

[0198] The MIC values (in mg/L) of representative compounds and of representative combinations including these compounds are listed in table 4. Table 4 lists the activity of the compounds of above formula I alone or in combination with β-lactamase inhibitors of formula II and formula III-XIII.

[0199] If in table 4 in the upper three rows a cell is left empty, then this means that in the combination of that column no compound of the category of that row was used.

Table 4: Activity of combinations of representative antibiotics

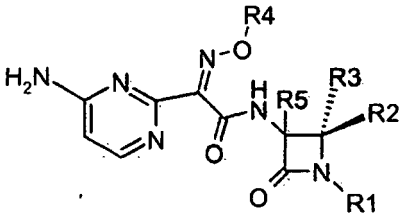
Antibiotic	1	1	1	1	1	1	1	1	1	1	1	1	20	20	20	20	20
β-lactamase inhbitor of formula II				102	102	103	111	202	206	323	323	324				102	206
β-lactamase inhibitor of formula V or VI		501	clavulanate	clavulanate	sulbactam	clavulanate	clavulanate	clavulanate	clavulanate	sulbactam	clavulanate	clavulanate		501	clavulanate	clavulanate	clavulanate
Bacterial strain	MIC (mg/L) of antibiotic at fixed inhibitor concentration of 4 mg/L																
Acinetobacter baumannii J2	>32	<0.06	>32	4	2	8	4	4	4	1	16	32	>32	<0.06	>32	>32	>32
Pseudomonas aeruginosa MK1184	>32	>32	>32	4	32	8	8	8	>32	4	16	8	>32	>32	>32	8	>32
Pseudomonas aeruginosa 1973E	16	8	8	2	4	4	4	4	4	4	8	8	16	16	16	32	16
Enterobacter cloacae P99	>32	16	32	4	8	32	4	16	8	4	4	4	>32	>32	>32	16	16
Klebsiella pneumoniae CF104	>32	0.5	0.5	1	1	0.5	<0.06	2	0.25	1	2	1	>32	16	32	2	4
Serratia marcescens S6	>32	4	4	0.25	0.5	0.25	0.25	0.5	4	0.5	0.25	1	4	2	2	0.5	0.5
Stenotrophomonas maltophilia 1AC736	1	0.25	0.5	0.125	2	0.125	0.125	0.125	0.125	0.125	0.125	0.125	4	0.25	0.25	0.25	0.5

Table 4 (continued)

Antibiotic of formula I	16	16	21	21	21	21	21	21
β-lactamase inhibitor of formula II		102		102	102	323	323	324
β-lactamase inhibitor of formula V or VI		clavulanate		sulbactam	clavulanate	sulbactam	clavulanate	sulbactam
Bacterial strain	MIC (mg/L) of antibiotic at fixed inhibitor concentration of 4 mg/L							
Acinetobacter baumannii J2	>32	16	>32	2	>32	2	8	2
Pseudomonas aeruginosa MK1184	>32	16	>32	32	16	8	32	32
Pseudomonas aeruginosa 1973E	>32	16	8	16	8	32	16	16
Enterobacter cloacae P99	>32	>32	>32	32	32	8	8	8
Klebsiella pneumoniae CF104	>32	32	>32	2	<0.06	1	2	4
Serratia marcescens S6	>32	>32	8	16	0.5	2	2	4
Stenotrophomonas maltophilia 1AC736	>32	2	8	8	2	4	2	4

Claims

1. A compound of the following formula Ib:

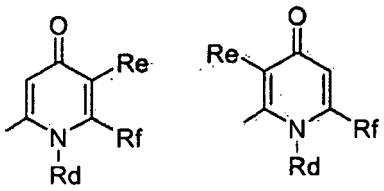


Ib

wherein

R1 is SO_3H;
R2 is H;
R3 is methyl;
R4 is C (Rx) (Ry) Z; whereby

Rx = Ry = H, and Z is a group of one of the formulae



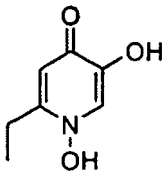
wherein Rd, Re and Rf are individually selected from hydrogen and hydroxy, with the proviso that at least two of Rd, Re and Rf are hydroxy; and

R5 signifies hydrogen;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein Rd and Re are hydroxy and Rf is hydrogen.

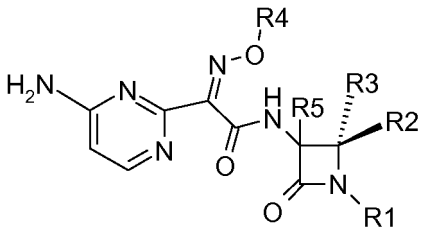
3. The compound of claim 1, which is a compound (21) wherein: R4 is



and R5 is hydrogen.

Patentansprüche

1. Eine Verbindung der folgenden Formel Ib:

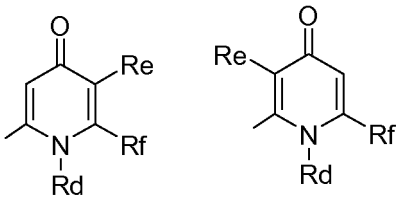


Ib

worin

R1 SO_3H ist;
R2 H ist;
R3 Methyl ist;
R4 C (Rx) (Ry) Z ist; wobei

Rx = Ry = H, und Z eine Gruppe von einer der Formeln



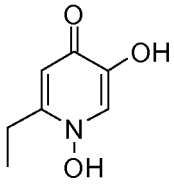
ist, worin Rd, Re und Rf unabhängig aus Wasserstoff und Hydroxy ausgewählt sind, mit der Massgabe, dass mindestens zwei von Rd, Re und Rf Hydroxy sind; und

R5 Wasserstoff bedeutet;

oder ein pharmazeutisch annehmbares Salz davon.

2. Die Verbindung nach Anspruch 1, worin Rd und Re Hydroxy sind und Rf Wasserstoff ist.

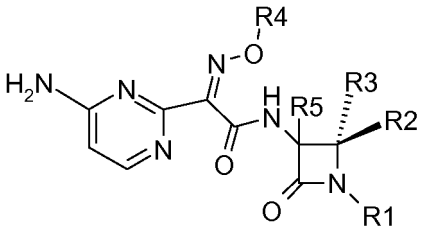
3. Die Verbindung nach Anspruch 1, die eine Verbindung (21) ist, worin R4



ist und R5 Wasserstoff ist.

Revendications

1. Un composé de la formule Ib suivante:

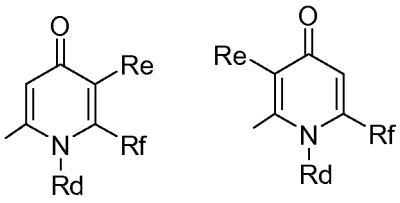


Ib

dans laquelle

R1 est SO_3H;
R2 est H;
R3 est methyle;
R4 est C (Rx) (Ry) Z; ou

Rx = Ry = H, et Z est un groupement d'une des formules



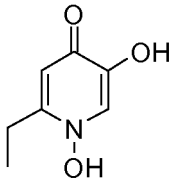
dans lesquelles Rd, Re et Rf sont choisis indépendemment parmi hydrogène et hydroxy, sous réserve qu'au moins deux de Rd, Re et Rf soient hydroxy; et

R5 signifie hydrogène;

ou un sel pharmaceutiquement acceptable de celui-ci.

2. Le composé de la revendication 1, dans lequel Rd et Re sont hydroxy et Rf est hydrogène.

3. Le composé de la revendication 1, qui est un composé (21) dans lequel R4 est



et R5 est hydrogène.

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